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AN ARTICLE CONTRIBUTED TO AN ANNIVERSARY VOLUME IN HONOR OF DOCTOR JOSEPH HERSEY PRATT

PROBLEMS OF ENDEMIC GOITER *

By FRIEDRICH VON MUELLER, *Munich*

THE two goiter conferences held at Berne in 1928 and 1933 revealed to the trained eyes of the participants the fact that in different countries, as, for example, in Munich, Berne, Vienna, Oslo and Utrecht, the clinical course and microscopic appearance of endemic goiter are quite variable. One dare not, for example, carry over and apply the experience of McCarrison or the Scandinavian countries to the endemic malady of the subalpine regions or, perhaps, the North American areas. The fundamental studies of the Swiss investigators and recently those of Dieterle and Eugster have shown that endemic goiter is locally confined to certain regions, villages and even houses. Further, it is not peculiar to the higher altitudes but rather occurs in the subalpine regions and gravelly areas about the streams which flow northward and southward from the Alps, as well as in the diluvial formations which represent deposits of the glacial epoch. Cretinism, the most baneful result of thyroid insufficiency, also occurs in the midst of this endemic goiter region. Endemic goiter in Europe is by no means entirely limited to the subalpine regions, for isolated areas where goiter is common are also found in Holland, along the North Sea coast, as well as in the valleys of the Oder, the Vistula and even the Saar. In the latter goiter areas, however, there is a striking absence of cretinism. The goiter which occurs in those endemic regions near the seacoast is, however, characterized by a great sensitiveness to iodine. Theodore Kocher has pointed out that true, genuine Basedow's disease occurs quite rarely in the subalpine endemic areas, while in the lowland plains of North Germany (i.e., in a country which is nearly free from goiter) it occurs not only much more frequently, but also in a much more malignant form. I have, myself, encountered the more acute forms of Basedow's disease which threaten the life of the patient, only in the regions of Northern Germany.

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Reports from the subalpine endemic regions indicate that even in new-born infants the thyroid glands are distinctly larger and heavier than those of the new-born in North Germany. Indeed, actual goiter occurs in the new-born in the subalpine regions. These thyroid enlargements of the new-born ordinarily present the picture of "parenchymatous" goiter, that is, with branching sacs rich in cells without follicle formation and without colloid. Further, experience has shown that even in endemic regions goiter of the new-born does not occur if the mother is given iodine during pregnancy. I possess such preparations of the thyroid gland of new-born infants from the endemic regions which were taken from children whose mothers had been treated with iodine and I was able to prove to my own satisfaction that in these cases the thyroid had a completely normal appearance, with follicles properly filled with colloid.

It is certain that endemic cretinism is closely associated with pathological changes in the thyroid gland. In about 90 per cent of the cases this takes the form of nodular goiter, often of considerable extent and showing severe degenerative changes. In about 10 per cent of the cases of cretinism there is no goiter, but rather we find almost complete absence of the thyroid. In these cases the thyroid gland is either quite undeveloped or, as the result of intra-uterine degenerative processes, it has been reduced to a small and compact solid mass. The most severe cases of cretinous degeneration are these with *athyrosis*.

It has further proved to be the case that in most cases of cretinism the *mother* likewise was goiterous. It cannot be concluded from this that both goiter and cretinism rest upon an inherited basis. The more probable conception is that the noxa of goiter, *the nature of which is unknown* to us, has acted during the course of the pregnancy, not only on the mother but also on the child in utero. As a consequence of our above mentioned experiences with the congenital goiter of the new-born, it may also be hoped that normal development of the thyroid gland may be achieved by means of the administration of iodine to pregnant women. In other words, the fight against cretinism must begin, not *after* the birth of the child, but rather while it is still in the uterus.

The administration of iodine to all women in the endemic areas is feasible only by means of the introduction of the use of iodized salt by the governmental authorities, for women frequently are unaware of a pregnancy and, further, the indolence of the inhabitants would prevent their carrying out iodine treatment of their own accord.

The question as to whether cretinism can actually be prevented by such radical measures is, however, still uncertain and the answer may never be known with certainty, more particularly because cretinism, for reasons unknown, has shown a substantial decrease during several decades.

In all the *milder* cases of cretinism, the condition is usually recognized first when the child enters school, at which time the waddling gait, the deeply depressed root of the nose and the defective intelligence become apparent.

At this time it is too late for iodine treatment, and the dried and powdered whole thyroid gland should be administered (not thyroxin); thereby very excellent results are often attained.

During the *school age* there very often appears an enlargement of the thyroid in children of otherwise healthy appearance. This goiter of school age gradually increases in size during the next few years. The goiter of school age is quite common in the endemic areas, as, for example, in Berne or in the Algäu, up to 80 per cent of all school children being affected. Experience shows this goiter of school age to be a harmless phenomenon which is almost never associated with signs of hyperthyroidism. It usually regresses spontaneously at the completion of puberty and responds exceedingly well to small doses of iodine. Because of this fact we have entirely given up the operative treatment of the goiters of school age and if such goiters become troublesome, they are treated with small doses of iodine, which may be given to the children by the school teacher in the form of iodosterin tablets, once a week. At about the twentieth year this adolescent goiter very often disappears entirely. Occasionally it persists to some degree, in which case the response to iodine is not nearly so good as is that of the true goiter of school age. At about the twenty-fifth year of life there often develops a certain hyperthyroid symptom complex. If, in the female sex, a pregnancy should occur at about the twentieth year, it is common for a swelling of the thyroid (as well as of the pituitary, as is well known) to become apparent. These *goiters of pregnancy* ordinarily are not accompanied by signs of either hypo- or hyperthyroidism and they usually react very favorably to small doses of iodine. *After* delivery they slowly regress during the subsequent weeks in the majority of cases and during this period the young mother at times notices weakness with tremulousness, physical and mental excitability and general loss of strength. This *asthenia of young women* often seems to be associated with the shrinking in size of the thyroid gland, together with some hyperthyroidism. In other cases the goiter of pregnancy persists and develops into a nodular goiter.

Since the goiter of school age, or adolescent goiter, is a harmless affair and responds brilliantly to iodine, the question arises as to whether iodine therapy is necessary at this age and whether it offers a dependable protection in later life. Is it possible for us to say that iodine therapy during school age gives us any prospect of a prophylactic effect against the later development of goiter or hyperthyroidism? I cannot answer this question in the affirmative. Indeed, I recall a number of cases where a youthful goiter was treated with good results and later during the thirties or forties a goiter appeared in spite of this fact, requiring operative interference. Further, we are unable to assert that the reduction of adolescent goiter to normal size and function constitutes a protection against the later appearance of Basedow's disease or of an iodine hyperthyroidism.

In the case of Basedow's disease, which I am unable to distinguish symptomatically from the so-called *Struma Basedowificata* or iodine hyper-

thyroidism, pre-operative preparation with Lugol's solution in doses which are not too small, in the manner introduced by Plummer, has shown itself to be of such value that at the present time it has been introduced in practically all surgical clinics. On the other hand, *prolonged* treatment of Basedow's disease with small doses of iodine, as recommended by Neisser, is rejected by most physicians and considered dangerous.

I conclude: In those regions of endemic goiter, in the midst of which cretinism is observed with a good deal of frequency, and indeed only in these, prophylaxis by means of the administration of iodine to pregnant women should be instituted by the authorities. This is certainly possible only through the substitution of iodized or complete salt for the ordinary table salt. In all other endemic goiter areas, on the other hand, the obligatory introduction of iodized salt is not desirable. The general use of iodized salt may be conducive to harm, in the case of older people or, particularly, to goiterous members of the family. The goiter of school age and adolescent goiter promptly regress under iodine therapy and almost never demand surgical interference. It is as yet, however, not certain whether the iodine treatment of adolescent goiter affords prophylactic protection in later life against the occurrence of goiter and hyperthyroidism.

AN ARTICLE CONTRIBUTED TO AN ANNIVERSARY VOLUME IN HONOR OF DOCTOR JOSEPH HERSEY PRATT

BLOODY PLEURAL FLUID, AN UNUSUAL COMPLICATION OF CIRRHOSIS OF THE LIVER *

By HENRY A. CHRISTIAN, F.A.C.P., *Boston, Massachusetts*

A NOTE on an unusual clinical picture is not inappropriate for a Festschrift to Joseph H. Pratt, who always has been an exponent of the art of being interested in the very unusual as well as the very common disease combinations of man. He is and always has been a keen clinician with an extraordinarily complete knowledge of medical bibliography.

An accumulation of pleural fluid in combination with cirrhosis of the liver appears to be not very unusual. Rolleston and McNee [1] quote Vedel and Puech as estimating it to occur in one-seventh to one-sixth of all cases, more often on the right than on the left side, often, according to them, as a manifestation of concomitant tuberculosis. However, a search through the Quarterly Cumulative Index back to its beginning in 1916 yielded only four titles (Salvatore,[2] Vedel and Puech,[3] Clerici [4] and Cassarini [5]) indicating papers on pleural fluid in association with cirrhosis of the liver. None of these were accessible to the author.

For the pleural fluid in patients with cirrhosis of the liver to be bloody in nature seems to be extremely unusual, since in this period no title could be found under either cirrhosis of the liver or various forms of pleural disease indicative of hemorrhagic fluid in the pleura in combination with cirrhosis of the liver. Rolleston and McNee speak of such hemorrhagic pleurisy as being of tuberculous origin, citing Barjon and Henry [6] and Jean [7] and reporting a case of their own, or as the result of alcoholism (Fernet [8]), or caused by trauma, citing a patient of theirs. The only case I have been able to find, independent of these factors, is one cited by them as reported by Taylor.[9] Examination of Taylor's report shows that a child of 13 with cirrhosis of the liver causing ascites, frequently tapped, developed near the end of life right-sided pain and a pleuritic rub with paracentesis the next day of nine pints of fluid. Two days later she died, and autopsy showed five ounces of blood-stained serum in the right pleural cavity, no evidences of pleural or pulmonary tuberculosis, normal heart and nodular cirrhosis of the liver. Taylor's title was "Cirrhosis of the Liver in Children; with Some Remarks on Cirrhosis"; here there is nothing to indicate description of so unusual a complication of cirrhosis of the liver; very probably other cases may have been reported equally buried under non-committal titles.

Recently I have had opportunity to observe a case of cirrhosis of the

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liver that, under observation, developed hemorrhagic pleural effusion requiring removal of paracentesis nine times before death.

The following gives the important data about this patient. A man of 60 entered the Peter Bent Brigham Hospital on November 13, 1936, complaining of jaundice of five weeks' duration and of enlargement of the abdomen of two weeks' duration. He had a history of excess in alcohol intake; no history of syphilis. He had been obese, now weighing 260 pounds after having lost 100 pounds in two years by dieting. Jaundice was marked, with dark urine and light stools for 11 days, and then cleared up to recur two weeks before admission, when his abdomen began to increase in size. On admission he was jaundiced (icteric index 70), obese with enlarged abdomen, dull in flanks and showing a fluid wave. His heart was not enlarged; there was a loud blowing systolic murmur over the precordium. Liver and spleen could not be palpated. Urine showed bile, at times albumin and very occasional cells and casts in sediment. Phthalein excretion was 90 per cent in 2 hours and 10 minutes; blood urea nitrogen 12 mg. per cent; plasma protein 5.7 gm. per cent with globulin 2.5 per cent and albumin 2.9 per cent. Blood showed a moderate anemia (85 per cent hemoglobin, 3,900,000 red cells) and a normal leukocyte count (7,800).

On December 7 physical signs of left-sided pleural fluid developed, and, on December 10, 900 c.c. of bloody, bile stained fluid were withdrawn, which had a specific gravity of 1.008 and contained 23,000 red and 2,000 white cells per cu. mm., 35 per cent lymphocytes and 65 per cent polynuclears. Tapping of left chest yielded bloody fluid as follows: December 15, 1,200 c.c.; 21, 800 c.c.; 28, 2,400 c.c.; January 7, 2,000 c.c.; 12, 2,000 c.c.; 23, 3,400 c.c.; 25, 1,600 c.c., the red cells progressively rising to 600,000 per cu. mm. On January 22 abdominal paracentesis yielded 3,100 c.c. of straw yellow fluid. As is so common in cirrhosis of the liver, from time to time fever developed, again to disappear. There was no apparent relation of the fever to the hemorrhagic pleural fluid. The patient grew progressively worse, and after five days of terminal fever died on February 6, 1937. Four roentgen-rays of chest, the first on November 20, when there was but a small amount of fluid in the left chest, never showed anything more than fluid and poorly aerated lung. Sediments from all nine specimens of pleural fluid were studied by methods of fixation and tissue stains; in the third, the pathological department made a diagnosis of tumor cells; no tumor cells were seen in the other eight.

The diagnosis in this case, particularly after the development of the hemorrhagic fluid in the left pleural cavity with its rapid reaccumulation, was actively discussed by the staff. At first the diagnosis of cirrhosis of the liver was held. With pulmonary and pleural signs appearing, it was thought that these resulted from a complicating inflammation. When the pleural fluid was found bloody and reaccumulated so rapidly, diagnosis veered to neoplasm, presumably primary in liver, as none could be demonstrated else-

where (negative roentgen-ray study of gastrointestinal tract; no evidence of prostatic tumor).

However, at a public clinic on February 4 the author of this paper expressed unequivocably his belief that the hemorrhagic pleural fluid was a result of the cirrhosis and was not of neoplastic origin and that the patient had cirrhosis of the liver of alcoholic etiology, in which possibly some lobules had undergone transformation into neoplasm.

The patient died two days following this clinic and autopsy revealed the correctness of the above diagnosis. There was no evidence that neoplasm or tuberculosis was responsible for the recurring hemorrhagic pleural fluid. The gastro-esophageal venous system did not appear abnormally dilated.

Summary

A case is reported of cirrhosis of the liver with recurrent left-sided bloody pleural fluid, the pleural condition not the result of neoplasm or tuberculosis.

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AN ARTICLE CONTRIBUTED TO AN ANNIVERSARY VOLUME IN HONOR OF DOCTOR JOSEPH HERSEY PRATT

THE GROWING IMPORTANCE OF CARDIAC NEUROSIS *

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I. INTRODUCTION

THE more heart disease there is, and especially the more widespread the publicity about it, the more important becomes the problem of cardiac neurosis. In fact it has assumed almost first place in our practice. Every week at least and sometimes daily for a while there are cases that must be carefully studied and treated with this point in mind.

The cardiac neurosis to which we refer is not neurocirculatory asthenia, which is not a mental and perhaps not even fundamentally a nervous state. We might better designate what we mean as *cardiac psychoneurosis.* It consists essentially of fear or apprehension about the heart, and it may be very severe and crippling. It is essential in the practice of medicine to recognize and to treat this condition early, for a long established cardiac neurosis may be almost incurable. The condition is increasing in frequency and is probably missed more often than any other cardiac diagnosis. It is time we laid the proper emphasis upon it.

Cardiac neurosis is always based on some very definite exciting factor. The occurrence of heart disease, especially heart deaths, among family and friends or even simply reported in the newspapers under dramatic headlines may initiate a cardiac neurosis in a person who is ready for a neurosis of some sort. The finding by a physician of a heart murmur, trivial or not, of some disturbance of rhythm which may be insignificant, of hypertension, great or slight, or of actual heart disease may be the exciting spark. A roentgen-ray report may unduly emphasize some unusual detail or an elec-

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trocardiogram may show an artefact or some slight deviation from the usual normal. Subjective sensations may be the starting point: a disagreeable extrasystole, a paroxysm of tachycardia, the manifold symptoms of neurocirculatory asthenia, sighing respiration, true dyspnea, angina pectoris, the prolonged pain of coronary thrombosis, and the various pains in the center or left side of the chest of noncardiac origin (due to cardiospasm, bursitis, muscle strain, and pleurisy among others).

It is not always appreciated that the family or friends of an individual suspected of having some heart trouble may become more fearful than the subject himself and actually need more attention from the physician. Only recently we have had the interesting experience of being consulted by a woman 60 years old without evidence of organic heart disease, who had travelled from a distance for relief of frequent crippling attacks of paroxysmal tachycardia which had not been adequately controlled by any kind of therapeutic measure that had been tried. No doubt the specific therapy that we advised may be equally unsatisfactory but one thing we did do, and that was to uncover and to help clear up the main difficulty, which was not heart disease itself, nor the paroxysmal tachycardia, nor even the patient's cardiac neurosis, but a rather severe neurosis of fear in several members of a large devoted family. This was the crux of the situation and the abolition of that fear should make a great difference in the attitude of the family toward her illness. Likewise, it is not uncommon to encounter cardiac neuroses in young people with or without heart disease, that have resulted from over-solicitude of anxious parents.

The most difficult cases of all are those with serious heart disease complicated by cardiac neurosis. It is a common experience in practice that nervous prostration or a severe cardiac psychoneurosis following coronary thrombosis, especially in physicians, is more difficult to treat than is the myocardial infarction itself.

We shall present herewith a few selected and striking examples of cardiac neurosis, with and without heart disease, four in whom the cardiac neurosis was the outstanding condition and, in contrast, one, with autopsy, in whom very extensive heart disease was for a long time masked by a psychoneurotic state. We have recently presented in the *Medical Clinics of North America*[1] several other cases illustrating cardiac neurosis in its various forms.

II. Case Histories of Patients with Cardiac Neurosis, with and without Heart Disease

A. Neurosis Predominating

Case 1. Neurosis Induced Largely by Neurocirculatory Asthenia. Normal Heart

A young unmarried teacher, aged 37 years, was examined by us on September 15, 1936. He had had scarlet fever at the age of thirteen. His father, a physician, is alive at 70 years of age, nine years after the onset of angina pectoris and seven years after coronary thrombosis; his mother, aged 66 years, is of a nervous disposition, has hypertension, and complains of much palpitation of the heart.

As a boy the patient noted that he could not keep up with his playmates because of palpitation and breathlessness. Consequently he avoided strenuous exertion and had always avoided it since. About 15 years ago he began to have some aching to the left and below the left nipple usually following exertion or nervousness, and often associated with rapid forcible palpitation. In 1930 he was seen briefly by one of us (who was caring for his father at the time) and found to have a normal heart and a blood pressure of 110 mm. mercury systolic and 70 diastolic. One month later, in September 1930, following unusual strain at his work, a period of nervous exhaustion and collapse occurred, associated with rapid palpitation (pulse rate 125 to 130). He went to bed with this illness, made a good recovery, and by December 1930 he felt quite well.

During 1931 he was in good health and able to play 18 to 36 holes of golf without difficulty, but he constantly took good care of himself. In 1931 he began to smoke cigarettes in gradually increasing numbers so that over a period of three years he was smoking as many as 30 a day. In February 1934 he began to find himself breathless on exertion (two flights of stairs) and to have palpitation and tachycardia as before. These symptoms, as well as some heartache, had continued unabated. During the year preceding his visit to us, he had taken on more strenuous work, had smoked heavily, and had found it necessary to give up golf and all other forms of exercise. The past summer had been particularly strenuous with teaching and lecturing and he had been under tension most of the time. With the aggravation of his former symptoms there had also been, on several occasions, pain in the left lower chest noted while riding over rough roads. He had also observed momentary "stopping of the heart" followed by a forcible beat. In July 1936 he began to have heartache and palpitation on retiring at night or on awaking during the night, particularly when lying on the left side. On July 10, 1936, he consulted a physician who told him that he had beginning angina pectoris and prescribed aminophyllin which was not taken. This diagnosis aggravated his symptoms further, increased his nervousness, and frightened him to such an extent that he resigned from the college where he was teaching and returned home on August 5, 1936. After a few weeks of rest at home he felt improved but he remained so worried over his condition that he insisted on being seen two weeks ahead of his scheduled appointment.

Careful questioning revealed no history of substernal pain. He was uncertain about radiation to the left arm and scapula, but frankly admitted that he had been looking for such radiation because he had heard one of us inquire about the characteristic radiation of the pain of angina pectoris in his father's case (coronary disease). He had also had access to medical books in which he had read about angina pectoris. Many physicians had assured him that his heart was normal, but the one who told him he had angina pectoris left the most profound impression. He was much depressed, wanted to know if he should claim disability benefits, and the inference was in talking to him that he had come home to die. He had taken bromides off and on for six years.

Physical examination revealed a heavy set man in apparent good health. The heart was normal in size, sounds, and rhythm. There were no murmurs. The pulse rate was 95. The blood pressure measured 132 mm. mercury systolic and 85 diastolic. Except for slight acne over the back there were no abnormal physical findings. The fluoroscopic examination and electrocardiogram were normal.

He was told that his heart was normal and given complete reassurance on this point along with advice to avoid fatigue of nervous origin, to limit tobacco to three or four cigarettes a day, to take only small amounts of coffee, and to exercise regularly.

When seen again on October 2, 1936, he reported that he had been completely well in the past two weeks since being reassured about his heart, that he had walked

as much as 10 miles a day, and that the pulse had been slower and the heart action quieter than for years. Physical examination again showed no abnormalities. The pulse was regular at a rate of 84. The blood pressure measured 120 mm. mercury systolic and 80 diastolic. He was reassured further regarding his heart and advised to continue as before.

In November 1936 it was necessary to reassure him once more of the unimportance of several vascular naevi that he had found on his skin after reading a medical reprint in which mention was made of spots on the skin in heart disease. In the latter part of December he reported a recurrence of many of his old symptoms in mild form attributed to increased nervous tension. By curbing his activities for several weeks these symptoms disappeared, and he is now in the good state of health which he enjoyed last fall.

Discussion. The factors in the background of the neurosis in this case are obvious, and it would have been surprising if, under the circumstances, a neurosis had not developed. In the first place, we are dealing with a nervous, sensitive individual with longstanding symptoms of neurocirculatory asthenia who had always protected himself from physical fatigue. Secondly, his family environment was such that heart trouble was ever in his mind, his father having had coronary disease for years, and his nervous mother having hypertension and heart symptoms. Moreover, he had ready access to medical books and journals. In the third place, he had been working recently under much nervous tension. Fourthly, he was a heavy smoker and it is common for the excessive use of tobacco to render a person more heart-conscious. And finally, and most important of all, he was badly frightened by an apparently "snap" diagnosis of angina pectoris made by a physician who was not well acquainted with him.

In treatment this case illustrates the good result of complete reassurance about the heart and sympathetic advice concerning his condition and mode of life. In such a patient, for a while at least, repeated doses of reassurance are usually needed, but always a careful and complete examination is essential at the start.

Case 2. Neurosis Initiated by Paroxysmal Tachycardia. Normal Heart

A 46 year old native housewife was first seen by us on February 17, 1936. Her family history was irrelevant. Her past history was unimportant except as it related to the present illness.

Fifteen years previously, about two months following the death of her only child, she was suddenly awakened one night by very rapid racing of the heart accompanied by severe pain in her left anterior chest. The pain was sharp and catching in character, was localized to an area about two centimeters in diameter over the fourth left costal cartilage, and was treated by the hypodermic injection of morphia. Following this, similar attacks of pain continued to occur at intervals of two to four weeks and were unrelated to exertion, emotional excitement, posture, meals, or respiration (except that during the pain she was unable to take a deep breath). The duration of the pain was from one minute to one hour, usually 15 to 30 minutes, and there was no radiation.

Relief usually followed the administration of morphia which had been given subcutaneously or by mouth for nearly every attack of pain. Nitroglycerine had

been tried but found ineffective. In December 1933 a brother, to whom she was much attached, died. Immediately thereafter her attacks of pain increased in frequency and severity so that she was confined to bed for 10 weeks. Since that time, over a period of about two years, she had had two to three attacks of "agonizing" pain daily, each requiring morphia (¼ to ½ gr.) for relief. Also during this time occasionally she had a sensation of fullness in her throat and palpitation. These symptoms frightened her and were attended by breathlessness and flushing of the skin.

From April 1935 to January 1936 she was under the care of a physician who was able to bring about some improvement with reassurance, phenobarbital, quinidine, and belladonna, and a reduction diet, but there were two marked exacerbations of symptoms in October 1935 and again in December 1935. It was at the latter time that she began to complain of oppression or constriction beneath the sternum, directly following the attacks of acute pain described above, and thought by the patient to have been relieved after 15 minutes by nitroglycerine. She complained now also of sharp discomfort in the region of the right scapula "like the pain of pleurisy" coming and going at times during the acute pain. Among other things she had been troubled by diarrhea for a "number of years." This had been aggravated by quinidine, but cleared up following the administration of dilute hydrochloric acid.

Repeated examinations by competent men failed to reveal any significant abnormality of the heart or nervous system and after 15 years of symptoms her general health remained unimpaired. Although the concensus among those who saw her was that her symptoms were functional in origin and aggravated by addiction to morphine, it was also agreed that she should be studied with the possibility of paravertebral alcohol injection of the thoracic sympathetic ganglia as a means of relieving her paroxysms of pain. Accordingly she entered the hospital under the care of Dr. J. C. White.

Physical examination on entry revealed a slightly obese woman, apparently well. The pulse was regular at a rate of 84. The blood pressure measured 118 mm. mercury systolic and 94 diastolic. The heart was normal in size and sounds. There were no murmurs. The examination showed no abnormalities except for quite marked precordial tenderness on light palpation.

The urine, blood, and stools were normal. A lumbar puncture revealed normal dynamics and a normal spinal fluid. The spinal fluid Wassermann was negative. The Hinton reaction of the blood was negative. The basal metabolic rate was minus 3 per cent. The electrocardiogram was normal except for slight left axis deviation consistent with her build. Roentgen-ray examination of the heart and lungs and of the dorsal vertebrae revealed no abnormality. A Graham test for gall-bladder disease was negative.

While under observation, many of her attacks coincided with visits by the attending physicians. A typical severe attack as observed by one of us was as follows. At the onset, she grasped the area beneath her left breast with her left hand and rocked back and forth groaning with pain. Respirations became deep and rapid. From her breasts up the skin became deeply flushed, and there was some mottling in the flanks, but the lower extremities were not involved. The temperature and sweating of the extremities were normal, but she perspired a great deal over the face and chest from increased exertion. Breathing later became shallow but remained forceful and rapid. The pupils remained intermediate in position. While listening to the heart over a period of three minutes the rate varied from 100 while holding her breath to 180 while at the height of a fit of sobbing and moaning. However, there seemed to be no relation between the severity of the pain, as manifested by her reaction, and the rate of the heart. At times she complained just as bitterly when the rate was 120 as when it was 180. The rhythm was regular throughout.

The blood pressure at the height of the attack measured 200 mm. mercury systolic and 100 diastolic. A ¼ grain dose of morphia quieted her within a few minutes and the pulse rate dropped to 100 with slight increases up to 120 as her sobbing and moaning gradually ceased. Forty-five minutes after the onset of the attack she was still holding her breast as if it ached but she was quiet and the pulse rate was 88. An electrocardiogram during the attack showed sinoauricular tachycardia, rate 130.

On February 19, 1936, Dr. J. C. White performed a left paravertebral novocaine block from the third to the sixth dorsal sympathetic ganglia, including the visceral rami, which gave good anesthesia over the area where she complained of pain. However, within 2½ hours, as sensation returned, she had another severe attack of pain, proving that her pain was not visceral in origin, because, under these circumstances, pain is consistently relieved for 24 hours or longer. Two days later the area of painful sensation in her chest wall was injected with novocaine during an attack, but without relief of the pain. Having thus demonstrated the futility of any neurosurgical procedure for the relief of her pain psychiatric treatment was recommended.

On September 15, 1936, her physician reported that after several months of sanatorium care her morphine addiction had been broken and that her precordial pain had nearly disappeared. She was doing nicely with an occasional placebo.

Discussion. This case is one of the utmost importance, for it represents a group of patients who have been unsatisfactorily diagnosed and handled. Her present illness dating back 15 years began apparently with a paroxysm of tachycardia attended by severe chest pain which awakened her one night shortly after the death of her only child. With this very first attack morphine was given and without careful analysis each succeeding attack was diagnosed as possible angina pectoris unrelieved except by morphine. In the first place it should have been quickly obvious that angina pectoris does not occur like this in a young woman and in the second place that angina pectoris does not require morphine. It is, of course, also important to note that nitroglycerine had been tried and found ineffective. A clue late in her disease was the exacerbation of her symptoms following the death of her brother to whom she was much attached.

It is quite probable, in fact certain, from our observations, that at least some and probably most of the so-called heart attacks were not of the nature either of paroxysmal tachycardia or angina pectoris. Early in her experience she had doubtless become sensitized by her original attack or attacks of paroxysmal tachycardia to any elevation of heart rate or increased force of heart action due to effort or excitement which would bring on a "heart attack" requiring morphine. The reaction in her case to any tachycardia might be considered a conditioned reflex. Repeated normal physical examinations and electrocardiograms made very unlikely a diagnosis of heart disease sufficiently serious to incapacitate her.

The most important factor of all in maintaining the prolonged psychoneurotic state was certainly the morphine therapy. She had become an addict. With morphine in the foreground, the background must always remain obscured no matter what the disease condition may be. The hysterical nature of the attacks with rapid relief by morphine bears witness to this.

Finally, the failure of the sympathetic and peripheral novocaine nerve block to relieve the attacks proves their hysterical foundation.

The cure of her morphine addiction has already resulted in improvement but emotionally she is still far from normal.

Case 3. Neurosis Induced by Sudden Knowledge of Compensable Heart Disease while in Army. Rheumatic Valvular Disease

A 29 year old native baker's helper who had not worked for 10 years on account of his health, was admitted to the Massachusetts General Hospital on March 14, 1936, complaining of attacks of precordial pain. He had had measles, mumps, and whooping cough in childhood, without significant complications. His appendix was removed in 1925 and the tonsils and adenoids were taken out in 1929. There was no history of rheumatic fever or chorea. He had smoked two packages of cigarettes daily until a short time before his entry to the hospital. One brother, a policeman, had been killed; another brother had died following the World War as a result of being gassed.

In 1926, while an enlisted man in the army, he had influenza; shortly following this illness he was declared completely disabled, because of heart trouble, by army physicians and given a medical discharge and a pension. One year later, in 1927, he began to have attacks of rather severe precordial pain, occurring once or twice a day, which he described as follows. The pain originated in the region of the apex of the heart, was dull, aching, and penetrating in character, radiated to the left shoulder and down the left arm to the hand, to the left chest posteriorly, and down the left leg to the knee. The attacks were of one to two hours' duration, were unrelated to effort, meals, or excitement, and were not relieved by nitroglycerine. Occasionally he was awakened at night by an attack of pain. In 1933, shortly after his government pension was entirely withdrawn, there was a sharp increase in the severity of his symptoms, which continued unabated coincident with his efforts to become reinstated on the pension list. In addition he began to notice moderate dyspnea, and rapid irregular palpitation on exertion, and with his attacks of pain. He had several severe nose bleeds in quick succession but no subsequent ones. For two years prior to admission he had had sudden syncopal attacks of unknown duration, occurring every three or four weeks, and followed for a short time by dizziness. He could suggest no precipitating factor for these attacks. For one year he had noticed slight pitting edema of the feet when he had been standing for an unusual length of time. For six weeks there had been fairly persistent nausea; he had vomited several times, and on three or four occasions he had suffered from severe frontal headaches lasting half a day. There was no orthopnea or cough.

Physical examination revealed a well developed and fairly well nourished young man with cyanotic lips. Breathing was normal. The heart was enlarged both to the right and to the left, the apex impulse lying in the midaxillary line, the right border of dullness 5½ cm. to the right of the midsternum in the fourth intercostal space. The heart action was forceful and the rhythm totally irregular. The rate was 80 at the apex and at the wrist. There were a Corrigan pulse and pistol-shot sounds over the peripheral arteries. At the apex there was a loud prolonged diastolic murmur, a loud slapping first sound, and a short blowing systolic murmur of moderate intensity. Fairly loud systolic and diastolic murmurs were heard at the aortic area and along the left sternal border. The aortic second sound was accentuated and greater than the pulmonic second sound. The blood pressure measured 140 to 120 mm. mercury systolic and 60 to 50 diastolic. The lungs were clear. The liver edge was just palpable beneath the costal margin and slightly tender. There was no edema of the extremities.

The urine, blood, and stools were normal. The Hinton reaction was negative. A teleroentgenogram showed dilatation of the heart slightly to the left and markedly

to the right. Oblique views showed marked prominence of the left auricle posteriorly and some prominence of the left ventricle posteriorly. There was also marked enlargement of the right ventricle. The aorta was small; the pulmonary vessels were only slightly prominent.

These findings we interpreted as those of mitral stenosis and regurgitation combined with an aortic lesion (aortic stenosis and regurgitation). The electrocardiogram showed auricular fibrillation, ventricular rate 80, slightly widened QRS waves (early intraventricular block), a tendency to right axis deviation, and a normal chest lead.

The concensus among most of the observers who saw him had been that his pain was that of angina pectoris of the type sometimes seen in patients with rheumatic heart disease and extensive aortic regurgitation, notwithstanding the fact that the mitral valve involvement seemed preponderant in this case. He continued to have attacks of pain while in bed under observation and over a period of two weeks he was given morphia rather freely for relief. On account of the severity of his pain paravertebral alcohol injection of the upper left dorsal sympathetic ganglia seemed justified to some of the observers. This procedure was carried out with some difficulty on account of unusually wide and thick transverse processes of the vertebrae, but finally, after three attempts, the first to the fifth left dorsal ganglia were satisfactorily injected. The resulting anesthesia over the left chest and vasodilation of the left arm and hand indicated a sympathetic block, which, in the experience of Dr. J. C. White, had usually been adequate to relieve pain in cases of true angina pectoris. However, the attacks of pain continued as before and it then became evident that he did not have angina pectoris.

In reconstructing the case at the time of our first examination after the events recorded above it was apparent that he was having an extreme reaction to the precordial discomfort induced by a very large heart thumping against his chest wall. There were good reasons for considering psychoneurosis as the chief diagnosis superimposed upon a background of organic heart disease. He had received a pension from the government for years and when this was discontinued his trouble increased. His pain was atypical of true angina pectoris, originating mainly in the region of the cardiac apex where the heart displaces the ribs, radiating even to the left leg, lasting for hours, unrelieved by nitroglycerine, and often requiring morphia for relief. His heart did not show the marked aortic regurgitation which has been almost invariably present in cases of angina pectoris in young persons with valvular heart disease and finally, alcohol injection of the upper dorsal sympathetic ganglia on the left gave no relief. This opinion is further borne out by the fact that he has continued unimproved since his discharge from the hospital.

Discussion. The neurosis in this patient was precipitated by the belated discovery of rheumatic heart disease when the patient was convalescing from a respiratory infection while in military service, and the importance of which was at once magnified by his immediate discharge from the service on pension. Any cardiac symptoms which this man had thereafter were naturally interpreted as serious.

The next step in his medical history was the marked exacerbation of his dolor pectoris following the withdrawal of his pension.

Then came the unfortunate label of angina pectoris to cripple him still more and, finally, to complete the picture there was the serious therapy consisting not only of morphine but also of the nerve injections. Confirmation of the diagnosis of psychoneurosis came with the failure of the nerve injections to give adequate relief.

Much time, money, and suffering could have been spared in this case by early recognition of the psychoneurosis and its proper treatment, chiefly by psychotherapy. It seems likely that even now the most effective measure would be the restoration of his pension. Such a thing as precordial rib resection might perhaps be advocated to give him subjective relief, but that is as yet an experimental measure.

Case 4. Neurosis Following Coronary Thrombosis

A 58 year old physician and naturalist was first seen by us on September 25, 1934, complaining of precordial oppression on effort. He had always had a "sensitive digestive tract" characterized by intestinal stasis and "auto-intoxication," but nevertheless he had been generally well and active. He had had pyelitis five years previously and severe whooping cough two years previously. He had used alcohol and tobacco heavily in years past, but both quite sparingly in recent months. He was overweight and had gained a few additional pounds recently. His father died of heart disease at the age of 46 years; his mother died of a "stroke" at 73 years of age.

For three and one-half years he had noticed on effort after meals an oppression in the left upper chest anteriorly radiating to the left shoulder and sometimes to the jaw, and relieved within a few minutes by resting. This symptom was somewhat worse after an attack of grippe nine months previously.

In May 1934, four months before his visit to us, he was awakened at 5.30 one morning by an attack of the chest oppression described above, which was, however, more severe than usual, lasting five hours, and requiring morphine for relief. He had a slight fever for several days, the blood pressure fell to 85 systolic, and the white blood cell count on one occasion shortly after the onset of these symptoms was 18,000. He spent three weeks in bed and then gradually got up and about. On July 5, 1934, six weeks after the onset of the prolonged pain, the blood pressure measured 125 mm. mercury systolic and 80 diastolic and a loud, late systolic murmur was heard at the cardiac apex by a consulting physician. The electrocardiogram at that time showed normal rhythm, rate 70, low voltage, late inversion of the T-waves in Leads II and III, and a normal Lead IV, altogether typical of myocardial infarction of the posterior or basal type. During his convalescence he had three or four brief attacks of chest oppression but none during the month preceding his visit to us. He felt well except for extreme nervousness and fearful apprehension about the consequences of his illness. He was afraid to be alone and insisted upon the constant presence and attentions of his wife. Because he had always led a fairly vigorous, physically active outdoor life, which he was now unable to do, his outlook was gloomy and he chose to look upon himself as entirely crippled and unable to carry on usefully.

Physical examination revealed a heavy set man in apparent good health, but somewhat nervous and apprehensive. The heart was normal in size, sounds, and rhythm. At the apex there was a slight late apical systolic murmur. The pulse rate was 80. The blood pressure measured 122 mm. mercury systolic and 80 diastolic. The lungs, abdomen, and extremities were normal. Fluoroscopic examination showed the heart to be normal in size and shape and the lung fields clear. The electrocardiogram showed normal rhythm, rate 85, low voltage, and low upright T-waves in the conventional leads, a very definite improvement as compared to the original electrocardiogram in July 1934.

It was apparent that he had done well following his coronary thrombosis and that the basis of most of his existing symptoms was fear and apprehension. He was therefore strongly reassured regarding his heart, advised to resume some of his hunting and exploration but to avoid strenuous effort, to spend his winters in an

equable climate, and to carry nitroglycerine with him should the occasion arise for its use.

He has been seen at intervals of six months since his first visit. During that time with much reassurance he has shown steady improvement and has been able to resume much of his former activity in his nature work outdoors. He still has some oppression in his chest on effort, particularly after meals or when nervous or fatigued, but he is able to get along quite well when he avoids exercise after meals and nervous tension. His physical, fluoroscopic, and electrocardiographic findings have remained much the same over a period of two and one half years. His mental attitude has improved greatly.

Discussion. Little or no discussion is required in this case. One need only emphasize that coronary thrombosis, no matter how mild, is very commonly accompanied and followed by mental depression and fear especially in a physician. This tendency is likely to decrease rapidly in the future with the current discovery of many cases with small infarcts, long survival, and unhampered physical reserve. This case illustrates also the value of some other interest than the particular occupation of the individual, some interest which is not fatiguing and which may continue to be cultivated for years.

B. Heart Disease Predominating

Case 5. Severe Coronary Heart Disease Masked by Psychoneurosis and Morphinism

A 34 year old manufacturer was seen by us on May 21, 1934. He had always led a strenuous life, smoked heavily, and had been under much nervous strain for years with family and community activities. He had had numerous illnesses and operations (appendix, tonsils, antrum, injured hands, and "adhesions"). In 1930 he began to take morphine for migraine and later it was necessary for him to take the cure at a sanatorium.

His father and mother died of heart trouble at the ages of 59 and 48 years respectively.

In July 1933 he strained himself holding back a car on a hill and was exhausted. He felt no pain then but on the following day his chest was lame in front and on the left side. Four days later he felt well and pitched hard in a ball game for seven innings, having to stop because of fatigue, and not because of pain. He was unable to play much golf for the next few days because of exhaustion. He then took a long train trip and two weeks after the ball game, while lifting his small son on the beach, he suddenly felt oppressive pain to the left of the upper sternum lasting five to ten minutes. This pain recurred at intervals throughout the day with increasing severity and duration until 9.30 p.m. when it became constant and required morphine, which gave him relief when given at 3 a.m. the following morning. An electrocardiogram taken several weeks after this episode showed definite evidence of myocardial infarction at the apex of the left ventricle.

After a prolonged convalescence with gradually increasing activity he returned to his former strenuous life about May 1, 1934. On resuming his usual activities he began to have sharp stabs of precordial pain several times daily at rest or on effort. When first seen by one of us he was under treatment for a renewed addiction to opiates.

On physical examination he appeared well but nervous and apprehensive. There was slight cardiac enlargement, confirmed by fluoroscopy. The heart sounds were

good, the rhythm regular except for an occasional premature beat, and there were no murmurs. The pulse rate was 90, the blood pressure measured 120 systolic and 75 diastolic. The electrocardiogram showed normal rhythm, rate 105, interrupted by one ventricular premature beat, flat T-waves in Lead I, and slight left axis deviation. A later electrocardiogram in September 1936 showed also an absent Q-wave in Lead IV, further confirmatory evidence of previous myocardial infarction.

It was the opinion of some of his medical observers that in spite of the definite evidence of coronary disease much of the precordial pain of which he complained was on a neurotic basis. After repeated medical investigations and prolonged rest without sufficient relief to allow him to carry on a comfortable and useful existence a diagnostic paravertebral novocaine injection of the upper dorsal sympathetic ganglia was done during one of his severe episodes of pain with almost complete relief within five minutes. He was so impressed with the relief obtained that he wished to have a resection of the sympathetic nerves no matter what the risk. This was attempted but he did not survive the operation. Postmortem examination disclosed extensive coronary sclerosis with old occlusion of the descending branch and thrombosis of the circumflex branch of the left coronary artery together with marked scarring of the left ventricle. There was a definite and pronounced aneurysmal dilatation of the anterior wall and apex of the left ventricle.

Discussion. This case is of the greatest interest and importance and without its inclusion our paper would be open to serious objection. It presents the other side of the picture from that illustrated in the first four cases. With a renewed enthusiasm in the recognition and treatment of cardiac neurosis one may easily go too far and fail to recognize the presence of serious heart disease that may lead to early death.

This patient's coronary disease was in large part overlooked or minimized for several reasons, consisting of his youth, his obvious nervousness, his addiction to morphine, and his relatively normal physical examinations. The electrocardiogram, however, proved to be of vital importance as it has been in most of our other cases of coronary disease in youth. It showed, without question, the presence of extensive myocardial infarction which was later confirmed at autopsy.

The case illustrates, incidentally, the danger of radical neurosurgery, in the presence of severe coronary disease, in contrast to nerve injections.

III. Summary and Conclusions

The growing importance of cardiac neurosis has impressed us with the need of its emphasis at the present day when there is so much publicity about heart disease. Every patient with cardiac symptoms or signs or with knowledge of heart disease in family or friends is a potential cardiac neurotic.

We have presented herewith five striking examples of cardiac neurosis. The first case had as a basis a hypersensitive nervous system, a history of heart disease in the family, access to medical literature, increased nervous tension in his work, and a hasty incorrect diagnosis of angina pectoris; the excessive use of tobacco may have been an aggravating factor. The second case was a young woman whose first heart attack, apparently consisting

of paroxysmal tachycardia with precordial distress, followed the death of her only child and was unfortunately treated with morphine; during the next 15 years she became a morphine addict and never showed any evidence of heart disease. The third case was a young soldier whose rheumatic heart disease was unfortunately discovered for the first time when he was suffering from neurocirculatory asthenia following influenza, and for which he was discharged as partially disabled from the army; an exacerbation of his symptoms followed some years later when his pension was discontinued and became so severe that it was confused with angina pectoris and treated with morphine and nerve injections. The fourth case is an illustration of the mental depression and neurotic apprehension which often follows coronary thrombosis; the patient was a middle-aged physician who made a striking gain after reassurance and the readjustment of his activities and interests.

It is obvious that the early recognition and proper treatment of cardiac neurosis by psychotherapy would have spared these four patients much time, money, and suffering. There are many other cases like these.

In contrast with these four cases we have presented one important example, case 5, of serious heart disease consisting of coronary thrombosis and myocardial infarction masked by psychoneurosis and morphinism in a young man whose electrocardiograms gave the necessary clues to the correct diagnosis.

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AN ARTICLE CONTRIBUTED TO AN ANNIVERSARY VOLUME IN HONOR OF DOCTOR JOSEPH HERSEY PRATT

AORTIC STENOSIS WITH SPECIAL REFERENCE TO ANGINA PECTORIS AND SYNCOPE *

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INTRODUCTION

THE accuracy of diagnosis, the interpretation of physical findings and the etiology, frequency and symptomatology of aortic stenosis have been matters of considerable controversy in recent years. About 30 years ago the diagnosis was often made on the basis of a systolic murmur over the aortic area without any other confirmatory evidence. It became particularly clear during the great war that this was entirely insufficient evidence to warrant the diagnosis, when in some army camps and in the hands of some boards that were examining recruits, large numbers of cases of aortic stenosis were being reported. Such cases were subsequently regarded as having neuro-circulatory asthenia, showing a basal systolic murmur frequently found in this condition. The result of this experience led to the view that still prevails in the minds of many, that aortic stenosis is rare. It will be clear from this study that the pendulum has swung much too far in this direction, and that many clinical aspects of aortic stenosis need reconsideration and reappraisal. Certainly it can be stated at the outset that aortic stenosis is a fairly common lesion, and that basal systolic murmurs cannot be dismissed lightly.

The purpose of this study is to review some of the clinical features of aortic stenosis that might help in diagnosis, and especially to discuss two complications to which attention has recently been called, i.e. the occurrence of syncope and angina pectoris.

Although there are numerous isolated references to aortic stenosis in the older literature briefly reviewed by Marvin [1] and Margolies,[2] it is only in the last decade that the importance of this lesion has been stressed. Cabot [3] in 1926 reported 28 autopsied cases. He called attention to the greater frequency of aortic stenosis in the male sex, the absence of evidence of aortic regurgitation in approximately half of the cases, and the occurrence of the disease predominantly in individuals past 40 years of age. Willius [4] studied 96 cases, and stressed the fact that anginal pain was a common occurrence in 21 per cent of his cases. Forty-six per cent also gave a clear cut history of rheumatic fever. Margolies [2] emphasized the frequency of calcification of the valve in aortic stenosis but regarded the process in the most part as

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sclerotic in nature. Christian [5] reported 57 cases that came to autopsy, 21 of which had calcification of the aortic valve. He also predicted that the calcification could be visualized by the roentgen-ray. McGinn and White [6] reviewed 123 cases of aortic stenosis that came to autopsy and 113 that were examined clinically. Only one-third of the cases that came to autopsy were accurately diagnosed during life. A definite history of rheumatic fever was obtained in 23 per cent of the autopsied group and 46 per cent of the clinical series. Faintness, dizziness or actual syncope were fairly common complaints, occurring in 22 per cent of the cases. Nineteen per cent had angina pectoris. Nine of the patients in their series died suddenly.

Marvin and Sullivan [1] reported 11 cases of aortic stenosis that died suddenly and presented the view that syncope and sudden death in cases of aortic stenosis may be due to a hypersensitive carotid sinus. Boas [7] discussed 19 cases, four of which had angina pectoris, and believed that the angina pectoris was due to the narrowing of the aortic valve. LaPlace [8] reported a series of cases of aortic valve disease and found that the degree of aortic regurgitation as measured by the diastolic pressure had no relationship to the presence of angina pectoris.

Material in This Study

In the selection of material for this review only those cases were included that could be regarded as having definite evidence of aortic stenosis. The three main criteria were the presence of a systolic thrill at the base of the heart, the detection of calcification in the aortic valve on fluoroscopic examination and the postmortem findings. All cases that had definite evidence of organic involvement of the mitral valve were excluded in order to study the features of aortic stenosis per se, eliminating any complicating events that the presence of mitral valve disease might entail. For this purpose all the clinical and pathological data in the records of the Peter Bent Brigham Hospital, from the year 1913 to 1935 inclusive, were analyzed together with the cases seen by one of us in private consultation practice. This comprised a group of 180 definite cases of aortic stenosis.

Etiological Considerations

It has been and still is often difficult to establish a conclusive relationship between an early rheumatic infection and a subsequent valvular lesion. There is no indisputable and constant pathological finding which determines the rheumatic nature of any cardiac abnormality. The presence of Aschoff nodules in the heart, although very distinctive, is often wanting, even when there is every reason to believe that the lesion is rheumatic. An early rheumatic infection may have taken on one of the many bizarre forms so that the proper diagnosis never was made. Even when the correct diagnosis was made the patient and his family may not have been informed of it. When a great many years elapse, as often happens, before cardiac embarrassment develops, the early diagnosis may readily be forgotten. Finally

a positive past history of a rheumatic infection and the presence of a valve lesion is not necessarily proof that the former is the cause of the latter. One is therefore left with opinions rather than with proof.

If specific diseases from a clinical point of view are rarely if ever associated with the subsequent development of stenosis of the aortic valve, it is reasonable to eliminate them entirely from our discussion of causation. In this group may be included pneumonia, typhoid fever, syphilis, and many other specific infections. It may be mentioned at this point that we did not find a single instance in which aortic stenosis could have been due to syphilis, notwithstanding the great frequency with which this disease produces aortic insufficiency and aortitis. It is not certain, however, how often nonspecific infections of a mild degree such as the "common cold," influenza or sore throat were the etiological cause of cases included in this study.

The great frequency of calcification of the aortic cusps naturally led to the belief in the past that in many instances it was purely arteriosclerotic. This opinion seemed to be further validated, in many instances, by the absence of any previous history of rheumatism or of any other significant infections. In refutation one might offer the evidence that is found in the mitral valve. Here stenosis occurs and is frequently accompanied by marked calcification, even in comparatively young people in whom very few would deny the rheumatic etiology. This often occurs when there is no available history of previous rheumatism. In fact it is a common experience to find calcification developing in any old and prolonged inflammatory process like tuberculosis, syphilis, parasitic cysts and other conditions. From the above considerations it follows that a particular lesion of the heart may be regarded as rheumatic in origin if an early history of rheumatic fever, chorea, or other stigmata of rheumatic disease are present in a large percentage of the cases, and if there is no other predominating etiological cause. It is well to recall that in a large series of cases of mitral stenosis, which all regard as almost invariably due to rheumatism, a history of this early infection can only be obtained in slightly more than 50 per cent of the cases. If a similar incidence can be found in relation to any other valve lesion it is equally logical to assume that rheumatic fever is the etiological factor.

In this series of 180 cases there was a definite history of rheumatic fever or chorea in 57 instances (31.7 per cent). The figures for the two sexes were approximately the same. The interval between the first rheumatic infection and the time these patients were first examined averaged 23.3 years for the females and 28.9 years for the males. The extremes were quite wide, from a few years to 60 years. This is considerably longer than similar figures would be for cases of mitral stenosis. In addition there were 23 in which the history was questionable. By this is meant that there was a history of previous "rheumatism," sciatica, growing pains, nosebleeds, etc., or that a heart murmur developed after an early acute infection. If these are included the total incidence would be 44.4 per cent. This corresponds fairly closely to the observations of Willius [4] who found a history

of rheumatic fever in 46 per cent of 96 cases of aortic stenosis. It is a somewhat lower figure than the 50 per cent that is generally found in cases of mitral stenosis. The difference in the two groups can readily be explained by the fact that aortic cases when detected are on the average 10 years older than those with mitral disease, the latter coming to a physician earlier in their course because of troublesome symptoms of congestive failure. The result is that the aortic cases have more frequently forgotten their early infections or these infections have occurred in an era when rheumatic fever was not so well understood.

From the above discussion it would seem logical to conclude that rheumatic fever is the most frequent and most important cause of aortic stenosis. Furthermore, we are of the opinion that arteriosclerosis and calcification are secondary manifestations superimposed on lesions due to rheumatic fever or to some other early nonspecific apparently mild infection.

Age and Sex

The age distribution in this group of 180 cases of pure aortic stenosis ranged from 13 to 81 years, with an average of 52.5 years. There were 108 males and 72 females, i.e. 60 per cent and 40 per cent respectively. The average age of the males was 53.6 years and of the females 51.4 years. There was no significant difference in the distribution of the two sexes in the various decades (figure 1) although the largest number occurred in

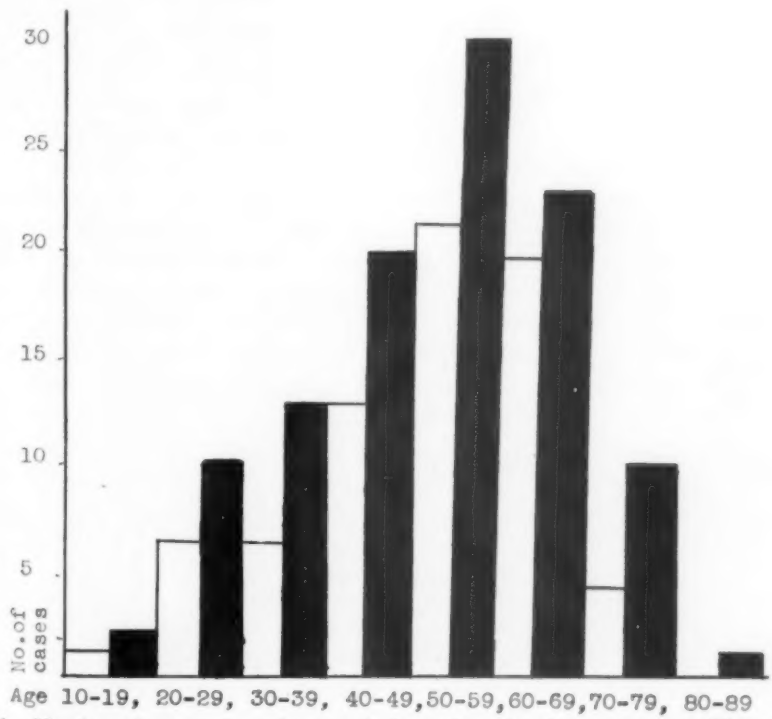

Fig. 1. Number of cases of aortic stenosis in various decades. ■ males; □ females.

the sixth decade. The incidence in the fifth and seventh decades was considerable. The number of females in this series was considerably greater than that reported by Margolies [2] or Willius,[4] but more closely approximated that given by McGinn and White.[6] The preponderance of males may possibly be explained by the greater frequency of chorea as the rheumatic manifestation in the female sex and by the fact that chorea rarely is responsible for subsequent aortic involvement.

Blood Pressure Considerations

The average blood pressure of 147 cases of aortic stenosis, in which readings were available, was 145 mm. of mercury systolic and 84 mm. diastolic. The range varied from a highest systolic reading of 260 mm. and a highest diastolic of 156 mm., to a lowest systolic of 80 mm. and a lowest diastolic of 10 mm. That hypertension was common is shown by the fact that there were 17 with systolic readings over 200 mm. and 22 with a diastolic over 110 mm. The average pressures for the 85 males was 138 mm. systolic and 79 mm. diastolic; that of the 62 females was 153 mm. systolic and 81 mm. diastolic (figures 2 and 3). This tendency for the females to have a higher blood pressure is in accord with findings obtained in a comparative study of the two sexes in relation to other forms of heart disease, such as mitral stenosis or angina pectoris.

There are two factors in addition to the stenosis of the aortic valve, which have some bearing on the blood pressure level. Insofar as there might be an accompanying aortic insufficiency there will be a tendency for the systolic pressure to be somewhat elevated and the diastolic to be depressed. Such effects are commonly observed in pure aortic insufficiency. The other factor is the one generally called essential hypertension, or that associated with an aging process. This will tend to show higher pressure readings in the older group. The common occurrence of hypertension in many types of cardiac disease makes one suspect that the intrinsic lesions of the heart may in some reflex fashion be partly responsible for hypertension. Another possibility is that the original etiological factor, namely rheumatic infection, may not only have been the cause of the valvular lesion but also may have produced changes in the peripheral vessels which eventually led to hypertension. The study of individual cases of aortic stenosis gives one the impression that when no other mechanisms are involved the systolic pressure is likely to be low and the diastolic slightly elevated, resulting in a small pulse pressure. Notwithstanding this, all ranges of systolic and diastolic levels from very low to very high may occur.

Physical Findings

Among the physical findings in cases of aortic stenosis there are some that are more peculiarly diagnostic of the anatomical lesion, and there are others less characteristic because of their common occurrence in a variety of other conditions. A systolic thrill in the aortic area, roentgen-ray evi-

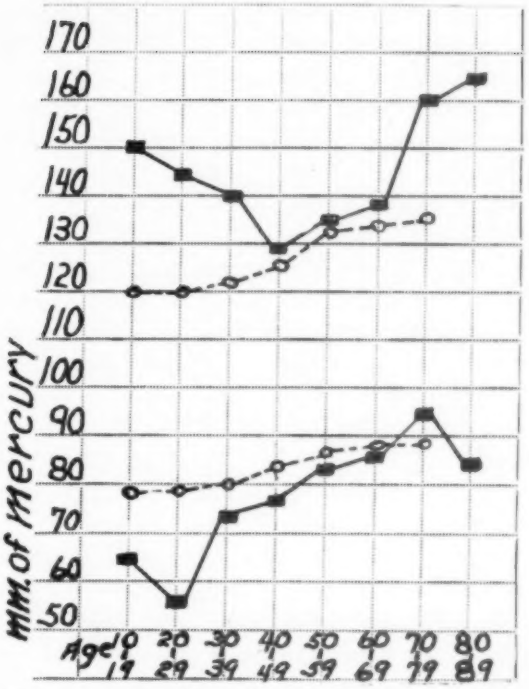

FIG. 2. Average blood pressure readings of cases of aortic stenosis (solid squares), as compared to normal individuals (circles). Male group.

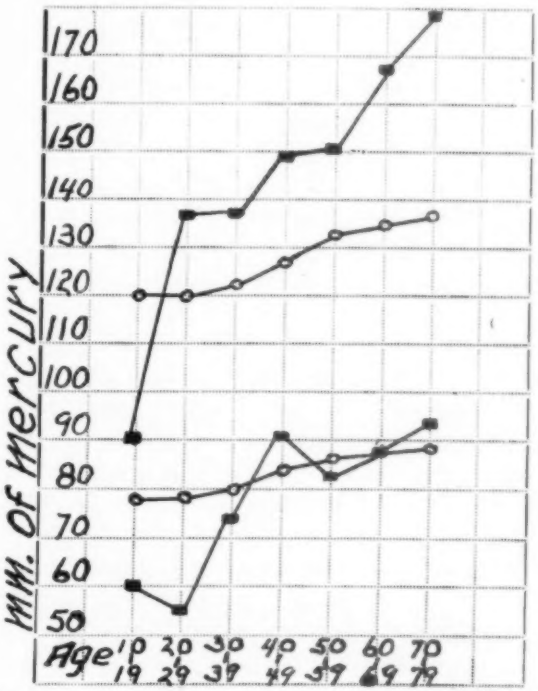

FIG. 3. Average blood pressure readings of cases of aortic stenosis (solid squares), as compared to normal individuals (circles). Female group.

dence of calcification of the aortic valve, a loud systolic murmur at the aortic area and a plateau pulse belong to the former group. Cardiac enlargement and an apical systolic murmur belong to the latter.

Cardiac hypertrophy is practically invariable in well marked aortic stenosis. In most cases this can be readily made out on physical examination, although during the early stages the percussion outlines do not always extend very much beyond normal limits. Marked dilation of the chambers such as occurs in mitral stenosis is not present as a rule, and therefore the cardiac silhouette is likely to be smaller, although the heart weight is greater in aortic stenosis than in mitral stenosis. In a previous study [9] it was found that the average weight of the heart in cases of aortic stenosis was 669 grams while in cases of mitral stenosis it was 474 grams. The great difference is due to the marked hypertrophy of the left ventricle of the former. When the left border of dullness does not extend much beyond the nipple line the finding of a forceful apical impulse will often indicate that there is considerable hypertrophy of the left ventricle. This type of impulse, which lifts the finger slowly and remains lifted for an instant before it recedes, is quite unlike the short snapping impulse that is found in mitral stenosis.

An apical systolic murmur is a quite common finding but one that is difficult to appraise. It can be partly due to a transmission of a loud basal bruit, and to some extent it may result from an accompanying mitral insufficiency, either relative or structural in nature. Its presence or absence does not aid in establishing or eliminating the diagnosis of aortic stenosis.

The most constant physical finding is a loud basal systolic murmur best heard at the second right interspace, or over the midsternum. This murmur is often harsh in quality but we feel that its intensity is of greater importance than its quality. In fact one may say that faint murmurs are rarely harsh. When the loudness of murmurs was graded from I to VI [10] as was done in many of the cases studied here, with rare exceptions the basal bruit was found to be of grade III intensity or louder. Often the apical murmur was just as loud as the basal and occasionally it was louder. There are other conditions in which loud systolic murmurs are heard at the base of the heart such as hypertension, congenital heart disease, anemia and hyperthyroidism. If these can be eliminated from consideration a loud aortic systolic murmur must always bring up the possibility of aortic stenosis. The direction of propagation of this murmur has been of no great aid in diagnosis. When loud it often could be heard throughout the chest, even in the right axilla. The importance of its transmission to the vessels of the neck has been exaggerated for this is due mainly to its intensity and to the proximity of its point of origin. There are occasional instances when the state of the circulation is so feeble that the murmur is quite faint and may only regain its loud and more characteristic intensity when the heart improves. It is in such cases particularly that roentgen-ray examination may be very valuable.

A blowing diastolic murmur heard in the second right interspace or along the left sternal border is a common, but by no means invariable finding in aortic stenosis. Stenosis of either the aortic or mitral valve frequently occurs without any auscultatory evidence of regurgitation. There are many instances of well marked mitral stenosis that show no systolic murmur whatever, and likewise many cases of aortic stenosis that have no diastolic murmur. In fact, of these 180 cases there were 87 in which no diastolic murmur was heard. To be sure this group excluded all cases with free aortic insufficiency, for this study was confined to well marked stenosis of the valve. In trying to elicit the aortic diastolic murmur, the fainter ones may be overlooked unless auscultation is carried out carefully, both in the recumbent and upright positions and during held expiration.

The most diagnostic physical finding is a systolic thrill. This is generally best felt at the aortic area but is occasionally present over the upper or midsternum and rarely to the left of the manubrium. A systolic impact must not be confused with a true purr that has duration, for when the latter is really felt and congenital heart disease can be ruled out a diagnosis of aortic stenosis is almost certain. There will be very rare exceptions when a loud basal systolic murmur and a definite systolic thrill will be found and yet stenosis will be absent. The explanation of such findings is still obscure. The difficulty is that in less than one half of the cases will a thrill be palpable.

In only 21 of the 51 instances in this series that came to autopsy was a thrill found. Possibly in some, more careful palpation might have been more successful. In others terminal cardiac weakness may have been the cause of the absence of this sign. The thrill is often overlooked because palpation is not carried out or because when a thrill is faint it may be detectable only in certain positions. It may be necessary to have the patient sit up or lean forward or even hold a deep expiration while the base of the heart is palpated.

No careful analysis was made of the frequency of an absent aortic second sound, or the reliability of this sign in the diagnosis of aortic stenosis. We are certain, however, that in some of the cases a clear second sound was heard in the second right interspace, although in many it was either diminished or absent. In according importance to the character of the second sounds at the base one should remember that the sound heard over the aortic or the pulmonary area is not necessarily made by the corresponding valve. In some obvious cases of hypertension the second sound is louder over the pulmonary than over the aortic area, although aortic pressure is considerably higher than pulmonary pressure. Likewise in some cases of aortic stenosis a second sound heard to the right of the manubrium may be partly a transmission from the pulmonary snap. In general it may therefore be said that the aortic second sound in these cases occasionally is present, though generally diminished or absent.

A plateau form of peripheral pulse has long been regarded as a characteristic of aortic stenosis. The frequency with which this peculiarity of the pulse is observed is diminished by the difficulty of its recognition and also by the fact that its typical form is commonly altered in the presence of an accompanying aortic insufficiency or hypertension. However, there are instances in which careful attention to the quality of the radial pulse may supply valuable supportive evidence.

A peculiarity of the pulse less generally appreciated is that the rate not infrequently is slow. This was quite well known to the clinicians of former times for Fothergill [11] in discussing aortic obstruction states, "the pulse is usually slow and steady." There are very few conditions apart from aortic stenosis in which the rate of the heart may be so slow in the presence of severe congestive heart failure, and where the slowing cannot be accounted for by a digitalis effect or heart block. This peculiarity on several occasions has been the first clue in reaching the correct diagnosis. The rhythm of the heart, unlike that observed in mitral stenosis, is generally regular. Of the 180 instances in this study auricular fibrillation was present in only 11 cases. Four of these were examined post mortem and none showed mitral stenosis. Factors such as age, sex, blood pressure and previous rheumatic infection were no different in the fibrillators than in those with regular rhythm.

Electrocardiographic Observations

In 82 cases electrocardiographic studies were made. Our findings concerning conduction disturbances were similar to those recently reported.[7] There were 14 instances of defective intraventricular conduction, including seven with typical bundle branch block. Three of the above 14 showed appreciable delay in the P–R interval and one had complete heart block. There were two additional cases of complete heart block. Conduction defects seemed to be more common in the cases of aortic stenosis that had angina pectoris than in those that did not have this complication. Eleven of the 82 cases had auricular fibrillation. Some of the others had extrasystoles of ventricular or nodal origin. It is significant that we did not have a single instance of right axis deviation in the entire series. If such a change in the electrical axis is found in aortic stenosis it should lead one to suspect an additional mitral stenosis. The main conclusion from the electrocardiographic studies is that defects in conduction are commonly associated with aortic stenosis.

Roentgen-Ray Findings and Calcification of the Aortic Valve

In the past there have been no distinctive roentgen-ray findings that characterized aortic stenosis. The boot shaped heart denoting a hypertrophied left ventricle, although common in aortic stenosis is also frequently present in pure aortic insufficiency and in some cases of hypertensive heart disease with left ventricular hypertrophy. Recently, however, the detection

of calcification in the aortic valve by fluoroscopic examination [12] has been of tremendous diagnostic value. This has invariably been indicative of a significant degree of stenosis of the valve. Inasmuch as this technic has been developed in the past several years, only 32 of the more recent cases of this series were fluoroscoped. Among these there were 26 instances in which this examination positively identified calcification of the aortic valve. Two of the remaining six were examined post mortem; one showed calcification, the other did not. It is evident that aortic stenosis may be present for a long period of time before calcification occurs in the leaflets. Such cases will necessarily be negative on fluoroscopy, and others may be missed because of the thickness of the chest wall or the faintness of the shadow. It also follows that calcification will be found more readily in the long standing cases. This is well borne out by the following figures. The average age of the group showing calcification was 60.3 years while that of the negative group was 42.6 years. The youngest of the positive cases was 45 years old, although younger individuals not included in this study have shown calcification of the valves by roentgen-ray. The value of roentgenographic examination is readily appreciated by the fact that in one half of the 26 cases, no aortic systolic thrill could be felt. In some of these the roentgen-ray was the only means of establishing the diagnosis. At present it may be stated that the roentgenological finding of calcification of the aortic valve is the most accurate single evidence of aortic stenosis, but that calcification may not be detectable during the early years of the production of this lesion.

The Occurrence of Angina Pectoris

Little mention was made in the older writings concerning the association of angina pectoris with aortic stenosis. Mackenzie [13] stated that, "there may be symptoms of angina pectoris but these are due to associated changes in the heart muscle." Recently more attention has been paid to this relationship.[6, 7, 14] The more recent teaching has been that although angina pectoris is commonly associated with aortic valvular disease it is due to insufficiency of the valve rather than to stenosis. The explanation that is offered for this association is that coronary flow takes place during diastole and that with the low diastolic pressure that accompanies aortic insufficiency there is inadequate flow through the coronary system with resultant relative myocardial anoxemia. This explanation is open to some doubt for there are those who believe that the main flow through the heart occurs during systole.[15] Apart from the theoretical controversy there are certain clinical experiences which make one doubt the accepted importance of aortic regurgitation in the production of anginal pain.

Free aortic insufficiency, syphilitic in origin, is rarely associated with angina except in those cases in which the coronary orifices are narrowed. Furthermore, as will be seen from the following data, angina occurs quite

commonly in aortic stenosis without any clinical evidence of insufficiency of the valve. The following explanation was kindly suggested to us by Dr. Tinsley R. Harrison: "The two important points about angina and aortic stenosis seem to be (1) that there is no evidence of anything which can decrease the circulation to the heart in these cases and (2) that in such patients there is much less relationship of the pain to exercise than in ordinary coronary angina. As regards the first point, while in cases without aortic stenosis one almost always finds at autopsy either coronary arteriosclerosis, luetic narrowing of a coronary orifice, or a well marked aortic insufficiency with a low diastolic pressure during life (the latter producing angina by causing interference with the blood supply to the heart during diastole), in persons with aortic stenosis typical anginal seizures may occur in the absence of any of these factors, the aortic insufficiency either not being present at all or in many cases of such mild degree as to cause no lowering of the diastolic pressure. In such cases the pathological evidence does not point toward a diminution in coronary flow and the enlarged coronary arteries suggest that the flow during life was actually greater than normal. However, this does not mean that the mechanism of angina is any different in such cases from that occurring in other patients. The coronary flow has to be looked at not per se but from the standpoint of its relationship to the need for blood; the latter of course depends on the oxygen consumption of the heart, which in turn depends largely on the work done by the heart. The latter depends on three factors—the amount of blood expelled per unit of time, the pressure against which this blood is expelled, and the energy expended in imparting velocity to this blood. As regards the output of blood, the only case which we studied had a normal cardiac output. However, the pressure within the ventricle during systole is probably enormously increased and this of course tends to increase the cardiac work. Furthermore, while the velocity factor is, under certain conditions, a relatively small fraction of the cardiac work, it may become the greatest factor in aortic stenosis, where with a markedly narrowed orifice the rate of flow must be enormously greater during systole. It is possible and indeed quite likely that the velocity factor is more than 50 per cent of the cardiac work in a case of marked aortic stenosis. Therefore, even though the coronary flow increases, say threefold, it is quite likely that the cardiac work may be increased four-fold, and this would of course tend to produce angina through the usual mechanism of myocardial anoxemia.

"As regards the second point; in the young patients with aortic stenosis we do not have pipe-stem coronaries but normal vessels which are capable of opening and closing. The attacks which come on at rest may very well be due to slight vasomotor changes in the caliber of the coronaries. Suppose that the arteries are wide open and are just able to transmit enough blood to prevent angina. Then even a very slight diminution in caliber could cause an attack. This is quite different from a normal person, where the arteries have large reserve and different from a person with extensive

coronary sclerosis where one can't imagine any opening and closing of the pipe-stem vessels."

Another explanation depends on the likeness of the aorta and coronary system to the common water faucet suction pump. The water flowing through the larger orifice causes a suction on the smaller orifice which enters it at right angles. The amount of suction is somewhat dependent upon the velocity of flow through the larger orifice. It seems reasonable to assume that in the normal heart with "paper thin" aortic valves, during systole these leaflets are fairly close to the coronary ostia preventing any such suction action. In cases of aortic stenosis with rigid, calcified immovable aortic valves, and markedly increased velocity of the blood flow, it is possible that this suction action may even draw blood out of the coronary arteries and lead to relative myocardial ischemia.

It was significant but by no means surprising that as many as 41 of the 180 cases, or 22.7 per cent had definite angina pectoris. (There were 28 additional questionable cases.) Of these 41 cases 22 were male and 19 were female; the average age of the former was 49 years (youngest 13 and oldest 64) and of the latter 59 years (youngest 25 and oldest 74). There was one case in the second decade, two in the third, three in the fourth, seven in the fifth, and the remaining 28 in the later decades. The average blood pressures for the two sexes in these cases were 136 mm. systolic and 80 mm. diastolic in the males, and 154 mm. systolic and 85 mm. diastolic in the females. These figures were similar to the blood pressure readings of the cases of aortic stenosis in general, but somewhat lower than those found in angina pectoris, unassociated with aortic stenosis.[16] It follows that hypertension is not a factor in the causation of angina associated with aortic stenosis.

The frequent absence of aortic insufficiency in this group with angina pectoris is indicated by the fact that in 19 of the 41 instances, no diastolic murmur was heard. This signifies that not only is pure aortic stenosis a common occurrence but that a concomitant angina is frequently present without an accompanying regurgitation.

To further validate this point of view 31 consecutive cases of free aortic insufficiency were studied. Only four were found to have angina pectoris and they were all luetic. Very likely the coronary orifices were involved in these. The average age of the 31 cases was 41.6 years and nine of them were over 50 years of age. The blood pressure readings in this group were typical of free aortic insufficiency, the average readings being systolic 154 mm. and diastolic 32 mm. In 15 instances a definite past history of rheumatic fever was obtained but the lesion had not progressed to detectable clinical aortic stenosis. The comparative rarity of angina in these cases of aortic insufficiency is in striking contrast to its frequency when the aortic valve is stenosed.

Inasmuch as the diagnosis of angina pectoris can only be made by a proper appraisal of the symptoms and because the subjective complaints that

lead to this diagnosis are often mild and may be over-shadowed by the more distressing breathlessness, the diagnosis is often overlooked. In many cases one has to initiate a direct inquiry into the possibility of any ill feeling in the chest on hurrying in the street, because the patient often will not spontaneously mention it. We feel that this type of careful questioning was responsible for the large number of cases of angina detected in this study. The importance of eliciting these symptoms lies in the fact that the frequency of angina throws some light on the prevalence of sudden unexpected death in aortic stenosis. Whenever the diagnosis of angina pectoris is correctly made one infers that that patient is subject to such a fatal outcome. It is interesting that of the 80 cases in which the type of death was known, nine dropped dead suddenly. In five of these nine cases a diagnosis of angina pectoris had already been made. We believe that in some of the others that died suddenly a diagnosis of angina pectoris could have been made if we had had the opportunity of inquiring carefully into the history.

One experience that we had bears directly on this point. A man of 50 entered the hospital complaining of increasing breathlessness. He showed the typical signs of aortic stenosis and marked congestive failure, and was studied most carefully by many physicians including ourselves. He improved on medical treatment and returned about one year later with recurrent failure. On this second admission a clear cut history was elicited by direct questioning of anginal distress, that antedated the first admission. It had been entirely overlooked by all members of the staff. After he had again recovered a fair degree of compensation and while feeling quite comfortable, he died instantly. If a proper history had not by chance been obtained he would have been classified in that vague group of cases of sudden death from aortic stenosis. Sudden death of this type can occur even in the very young who have aortic stenosis and angina pectoris, as was the case in a boy of 15 in whom both of these diagnoses were made, who dropped dead while going to school.

The duration of life in cases of aortic stenosis after the development of angina pectoris is not very different from what is found in ordinary angina. In the 19 patients of this present series who were known to have died, the duration of life after anginal pain first occurred was 3.3 years. Of 10 who were known to be still alive the duration was 5.5 years. The cases varied considerably and were too few in number to permit drawing any clear cut conclusions, but we have the general impression that the young rheumatic aortic case with anginal pain may carry on many years, although typical sudden fatality may occur at any time.

Syncope

The occurrence of syncope in aortic stenosis was lost sight of until a few years ago. This was recently discussed by McGinn and White [6] and in greater detail by Marvin and Sullivan.[1] Knowledge of the rôle that the

carotid sinus may play in the production of syncope,[17] naturally led to the suspicion that this same mechanism might account for the dizziness and fainting attacks that occur in aortic stenosis. With this in mind an investigation was carried out to test the irritability of the carotid sinus in some of these cases. In 19 a test for carotid sinus irritability was performed on each side and in none were positive results obtained for syncope, or dizziness was not produced.* Among these were two with a clear cut history of syncopal attacks. From this it seems unlikely that carotid sinus irritability can be a common occurrence in aortic stenosis or that it will explain, in the majority of cases, either the dizziness and fainting, or the sudden death. The possible rôle of the carotid sinus cannot be dismissed entirely, however, and further investigation is necessary. It is possible that reflex inhibition of the heart from a sensitive carotid sinus may be the cause of sudden death in rare instances. A more likely cause of sudden death is the same mechanism that prevails in ordinary angina. This assumption is particularly applicable in those cases in which the diagnosis of angina pectoris can be made. One may even postulate that some of the others die suddenly in their first attack of angina.

An attempt was made to detect clinical features which were characteristic of cases showing syncope or dizziness. There were 21 instances of true syncope and an additional 16 had significant dizziness without syncope. The average age of those with true syncope was five years greater among the males and 10 years greater among the females than the general averages. Despite their more advanced years those with syncope tended to have a somewhat lower blood pressure. Although these two differences were not great they may have some bearing on the production of the cerebral symptoms since both age and lower blood pressure may predispose to cerebral anoxemia.

Type of Death

Ninety-five of 180 cases studied were known to have died. Of these 18 died of unknown cause, 44 died of congestive heart failure, 15 of subacute bacterial endocarditis, four of coronary thrombosis, two of cerebral accidents, two of pneumonia and one of Adams-Stokes disease. The remaining nine died suddenly and unexpectedly. There were some differences in age between these various groups. Although the average age at death of all the fatal cases was 51.3 years, the group with subacute bacterial endocarditis died at an average age of 36 years. Those that died suddenly had an average age of 45 years. The three most common types of death are congestive failure, subacute bacterial endocarditis and angina pectoris.

It is of some interest to analyze the duration of the more important subjective symptoms and objective findings in the group of fatal cases. Such an analysis gives one a guide as to the prognosis when particular

* Since this study was completed two cases of aortic stenosis were seen without any previous history of syncope or dizziness that showed definite positive reactions to carotid sinus stimulation.

features develop in the progress of the disease. Palpitation of the heart was an early complaint and the average duration of life after its onset was eight years. Dyspnea on the other hand came much later, as the average length of life after its first occurrence was only 23 months. The average period of survival after edema was 9.3 months and after appearance of syncope 9.1 months. Syncopal attacks that occurred early in life, 15 years or so before the patient was seen, were disregarded as they were considered to be unrelated to the disease. The duration of life after congestive râles were found in the lungs and definite pitting edema of the legs occurred was 6.3 and 4.3 months, respectively. In many of these cases the features just enumerated may have been present for some time before they were first noted, but in general it may be said that life expectancy is quite short once clear cut heart failure has developed.

Diagnostic Considerations

The more important diagnostic findings in aortic stenosis are a loud systolic murmur at the base of the heart, a basal systolic thrill, a plateau pulse and calcification of the aortic valve on fluoroscopic examination. The presence of a true thrill or calcification by roentgen-ray are quite reliable diagnostically. The other two features are not as trustworthy. This explains the difficulty in diagnosis and the fact that the majority of cases are overlooked. It is obvious that a fair degree of stenosis must exist for years before all the above criteria will be apparent. The early stages of the process must therefore be diagnosed on data that have been regarded in the past as inadequate. In a previous publication [10] attention has been called to the importance of interpreting the presence of a systolic murmur as a possible early sign of aortic stenosis. In fact it was found that during the early stages a moderately loud systolic murmur that eventually proves to be due to aortic stenosis could be somewhat louder at the apex of the heart or the mid-precordium than in the aortic area. Also some cases regarded as having benign or insignificant systolic murmurs eventually prove to have aortic stenosis. With this in mind an analysis was made of 16 cases seen by one of us over the course of years, that eventually proved to have definite aortic stenosis but that had previously been misdiagnosed. Four of these were thought to have had mitral insufficiency, four aortic insufficiency, one a normal heart with a benign systolic murmur, six hypertensive heart disease and one chronic myocarditis. In none of these was a systolic thrill present at first, but in all either a systolic thrill or calcification of aortic valve or both developed. In conclusion it may be emphasized that loud basal systolic murmurs, especially in the absence of hypertension, must lead one to suspect the presence of aortic stenosis and make one search all the more diligently for other more convincing evidence.

Postmortem Findings

The main pathological finding that was investigated in this group of cases was the condition of the coronary arteries. The question naturally arises whether angina pectoris which accompanies aortic stenosis is due to atheromatous changes in the coronary arteries similar to those seen in patients without aortic stenosis or to the valvular lesion itself. The frequent occurrence of pathological changes in the coronary system in older people makes it necessary to appraise this problem in the younger group.

There were nine cases in this study with angina pectoris that were examined post mortem. Six were over and three were under 50 years of age. Two of the older group, aged 71 and 66, merely showed minimal changes in the coronary arteries without any narrowing of the vessels or infarction of the heart muscle. One case, aged 52, showed moderate sclerosis with narrowing of the coronary arteries and no myocardial infarction. Another, aged 66, had marked sclerosis and narrowing of the vessels with several small old infarctions. There was one, aged 62, that showed typical coronary thrombosis with infarction of the ventricle. The last one of this group, aged 52, had syphilitic aortitis, almost completely occluding both coronary orifices. Two of the younger cases, aged 46 and 25, had perfectly normal coronary arteries and the third, aged 46, showed moderate coronary changes without narrowing of the vessels. None of the last three had any old or recent infarctions of the ventricle. The complete absence of any alterations in the coronary system in two of the younger cases and the occurrence of only minimal alteration in some of the others, we consider as adequate proof that the anginal attacks were due to some other cause. It is more logical to regard this other factor as the actual valvular lesion. How this burden may be conducive to anginal attacks has previously been discussed.

Another pathological finding of interest is the localization of the calcification to the aortic valve and the ring. The deposits did not extend up to the mouth of the coronary vessels, which were distinctly free and open. In fact many cases of aortic stenosis, even in the older group, were comparatively free of atheromatous changes in the wall of the aorta itself.

Summary

1. A study was made of 180 cases of aortic stenosis, unassociated with any other significant valve disease, 53 of which were examined post mortem.

2. Evidence was presented to indicate that the etiology in most instances was a previous rheumatic infection. It was thought that some early ill defined infections may have been the cause in a few cases.

3. It was found that although the male sex predominates, the ratio was not more than three to two. The largest number occurred in the sixth decade.

4. The average blood pressure of the males was 138 mm. of mercury systolic and 79 mm. diastolic, and for the females 153 mm. systolic and

81 mm. diastolic. The range of these readings, however, varied from very low to very high systolic and diastolic levels.

5. The most distinctive physical findings in aortic stenosis were a loud basal systolic murmur, a systolic thrill near the aortic area, and the detection of calcification of the valve on fluoroscopic examination. In about one half of the cases no aortic diastolic murmur was audible.

6. Disturbances in conduction such as bundle branch block and auriculo ventricular block were quite common.

7. Twenty-six of 32 cases that were examined showed calcification of the valve fluoroscopically.

8. Angina pectoris was found to be quite common, occurring in 22.7 per cent of the cases. There is reason to believe that many cases are overlooked because of inadequate histories. An explanation of the possible mechanism of angina in these cases, not dependent upon coronary sclerosis was suggested.

9. There were 21 instances of syncope in this series. In four of these and 15 other cases the sensitivity of the carotid sinus was tested and found normal. It was found that sudden death occurred particularly in those with an anginal history, and that the carotid sinus was an unlikely cause of such eventuality.

10. The three most common types of death were congestive heart failure, subacute bacterial endocarditis, and sudden death. Once major symptoms developed in this group the average life expectancy was short.

11. Although the finding of a basal systolic thrill or calcification on roentgen-ray examination are very reliable evidences of aortic stenosis, the diagnosis in many cases and especially during the early stages, will have to depend upon the intelligent appraisal of a moderately loud basal systolic murmur.

12. A study of the postmortem material showed that the calcification is limited to the valve and does not involve the coronary orifices. The finding of normal coronary vessels in two of the young patients who had angina, and the presence of only minimal atheroma in the vessels of some of the others that had angina strongly suggest that the deformity of the valve itself is in some way responsible for this complication.

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AN ARTICLE CONTRIBUTED TO AN ANNIVERSARY VOLUME IN HONOR OF DOCTOR JOSEPH HERSEY PRATT

CHLOROSIS *

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CHLOROSIS is defined by Patek and Heath [1] as "a hypochromic anemia in adolescent girls and young women, usually associated with gastrointestinal and menstrual disorders." According to many observers, Naegeli [2] and Witts [3] among others, this condition, previously common, has become a disease largely of historical interest. Many of the younger clinicians who have not seen typical cases of classical adolescent chlorosis are inclined to doubt altogether the existence of this type of anemia. There is no doubt that chlorosis was quite frequent a quarter of a century ago. Its high incidence then, however, was more apparent than real. This is obvious from von Hoesslin's [4] critical analysis of 143 cases diagnosed as chlorosis. Of these 64 had histories suggesting tuberculosis; 25, gastric ulcer; 13, psychoneurosis; 13, secondary anemia due to endocarditis or other infections, and 5, excessive blood loss. The remaining 23 cases might have been called "possible chlorosis."

There are three factors responsible for the remarkable decrease in the frequency of this disease. The first is the introduction of more accurate diagnostic methods in the beginning of the twentieth century: the improvement in the chemical tests for occult blood in stools by Weber [5] who introduced the guaiac test, and by the Adlers [6] who introduced the benzidine test; the discovery of the roentgen-ray by Conrad Roentgen in 1895; the introduction of accurate methods for hemoglobin determination by Gowers,[7] Veillon,[8] Tallquist,[9] Dare,[10] Haldane [11] and Sahli.[12] Thus many cases previously diagnosed as chlorosis were discovered to have tuberculosis or some bleeding lesion in the gastrointestinal tract. A number of apparently pale patients were found to have normal hemoglobin values. The second factor is the improvement in the general and personal hygiene of the population. The third is the placing of many mild and some severe cases of chlorosis in the categories of nutritional anemias or microcytic anemia with achlorhydria.

Three cases of apparently classical adolescent chlorosis were seen by me recently. In view of the supposed rarity of this type of anemia the cases are presented here somewhat in detail.

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Case Reports

Case 1. A girl, aged 19, was first seen in November 1936, complaining of weakness, some shortness of breath, palpitation and vague pains in the lower abdomen. She was born in Scotland and came to the United States at the age of two years. She was born at term and was of normal weight at birth. She received neither orange juice nor cod liver oil during early infancy. Her appetite has always been capricious and her diet grossly deficient in green vegetables and meats. At the age of five years she was told she was anemic and was given some medicine for the anemia; this she took for a short time. At the age of 10 years she was told again by a physician that she was anemic; this time she took the prescribed medicine for about one month. Her menses began at the age of 14 years, have always been very scanty, particularly during the past year.

There was no history of any previous serious illnesses or operations.

On examination the patient appeared well developed and plump. She had a temperature of 100° F. (37.8° C.) by mouth. The skin was strikingly white. The face was definitely puffy. The sclerae were not icteric. The mucous membranes of the mouth were very pale. The tongue appeared normal. The heart was normal except for a soft systolic murmur over the mitral area. Examination of the lungs, abdomen, pelvis and rectum was negative. The extremities were negative except for some pretibial pitting edema. The finger nails appeared rather thin.

The urine and stools were normal. Analysis of the fasting gastric contents revealed complete absence of free hydrochloric acid. After histamine injection the free hydrochloric acid rose to 10 units. The blood Hinton reaction was negative. The other initial laboratory findings are presented in table 1.

Table I

Initial Laboratory Findings in the Three Cases of Chlorosis

Case	Red blood cells per cu.mm.	Hemoglobin, per cent (Sahli)	Mean corpuscular volume of red cells, cu. microns	Average diameter of red cells, microns	White blood cells per cu. mm.	Differential leukocyte count, per cent				Platelets per cu.mm.	Plasma proteins, grams per cent			Icteric index
						Polymorphonuclears	Lymphocytes	Monocytes	Eosinophiles		Total proteins	Albumin	Globulin	
1	4,920,000	52	67.0	7.21	10,750	69	16	11	4	2,671,000	5.6	3.1	2.5	5
2	4,440,000	55	—	6.66	7,500	58	35	5	2	499,000	4.7	2.7	2.0	5
3	4,160,000	50	—	6.74	6,300	55	37	6	2	1,467,000	6.3	3.1	3.2	5

The stained blood films of all three cases revealed small, pale red cells showing moderate anisocytosis and poikilocytosis.

This patient improved fairly rapidly under iron medication. The duration and quantity of her menses became more normal. The subsequent changes in the various blood constituents are presented in chart 1.

Case 2. A girl, aged 19 years, was first seen by Dr. Frank Mirabello in November 1936. She complained then of a mild "head cold." She was born in Nova Scotia and had been in the United States for three years. She was born at term and had normal weight at birth. Her diet has always been adequate. Her menstruation began at the age of 13 years, and the quantity, duration and recurrence of the menses have been apparently normal.

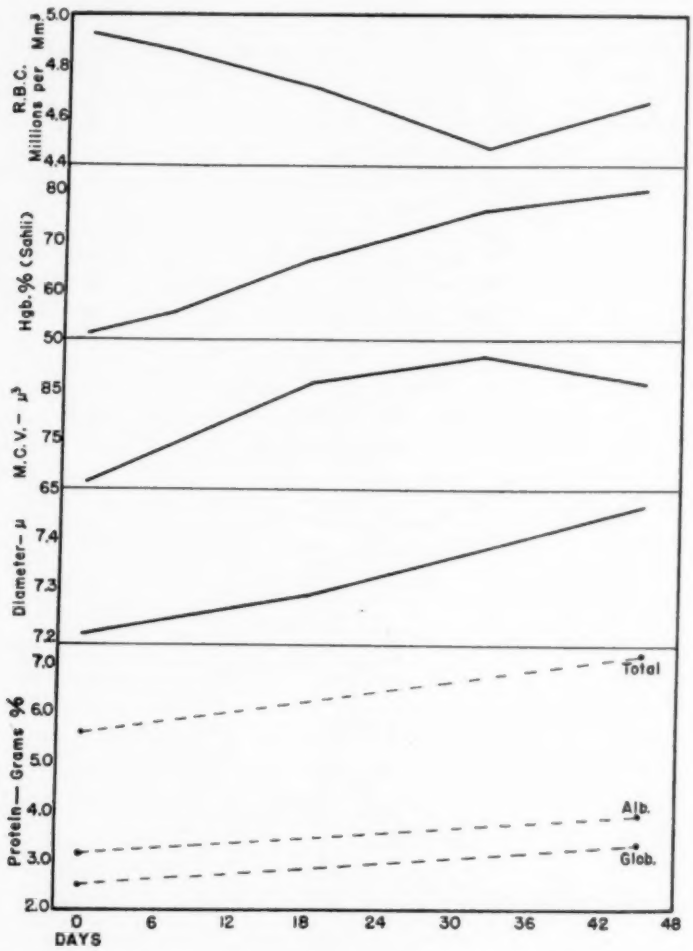

CHART 1. The behavior of the red blood cell count, hemoglobin, mean corpuscular volume of the erythrocytes, average red cell diameter and plasma proteins in case 1 under iron therapy.

On examination the patient appeared well developed, but rather thin. There was slight swelling and reddening of the mucous membranes of the nose and some generalized injection of the throat. The temperature was normal. There was moderate pallor of the mucous membranes of the mouth. The tongue was normal. The heart, lungs, abdomen and extremities were negative. The finger nails were normal.

The urine and stools were negative. Gastric analysis revealed complete absence of free hydrochloric acid after a caffeine test meal. The blood Hinton test was negative. The remaining initial laboratory findings are given in table 1.

This patient improved rapidly with iron medication. At the end of five weeks the red blood cell count was 5.33 millions per cubic millimeter, hemoglobin 82 per cent (Sahli).

Case 3. This patient is a twin sister of case 2. The history she presented is identical with that given by her sister. She was seen first by Dr. Mirabello in November 1936, complaining then of a mild acute upper respiratory infection. On examination the patient appeared well developed and well nourished. There was slight swelling of the nasal mucous membrane and slight reddening of the throat. The temperature was normal. There was moderate pallor of the mucous membranes of the mouth. The tongue was normal. The heart, lungs, abdomen and extremities were negative. The finger nails were normal.

The urine and stools were negative. Gastric analysis revealed post-histamine achlorhydria. The blood Hinton reaction was negative. The remaining initial laboratory findings are presented in table 1.

This patient improved rapidly under treatment with iron. At the end of five weeks her red blood cell count was 5.4 millions per cubic millimeter and the hemoglobin 74 per cent (Sahli).

The most significant deviations from the normal in patients with chlorosis are to be found in (1) the gastric secretions, (2) the blood plasma proteins, (3) the red cells, and (4) the blood platelets.

Gastric Secretions. It is frequently stated that in chlorosis hyperacidity is common and achlorhydria rare. However, one of my patients revealed hypoacidity after the injection of histamine; another, achlorhydria after a caffeine test meal and the third, complete post-histamine achlorhydria. Of Patek and Heath's [1] four cases, one exhibited normal gastric secretion, two hypoacidity following histamine injection and one complete post-histamine achlorhydria. It would seem, therefore, that hypoacidity and even complete post-histamine achlorhydria are not rare in chlorosis.

Blood Plasma Proteins. It has been pointed out (Naegeli,[2] Brugsch [13]) that in this disease the total plasma proteins may be reduced with the albumin-globulin ratio remaining normal. Two of my patients showed a reduction in the total plasma proteins. Decrease in the plasma proteins has been noted, however, in other types of anemia and has been observed also by Wintrobe [14] in primary hypochromic anemia. When the reduction in the plasma proteins is considerable, edema may appear. However, the production of edema is not dependent solely upon the actual level of the plasma proteins (critical level is 5.5 ± 0.3 per cent, according to Moore and Van Slyke [15]), although this constitutes the most significant single factor. There are other factors, such as the total fluid intake and sodium chloride intake, which may play important rôles. It is perhaps for this reason that case 1 with a total plasma protein of 5.6 grams per cent exhibited edema, while case 2 with a total plasma protein of 4.7 grams showed no edema whatever.

Red Cells. The total red cell count is frequently normal or even elevated above the normal level. The erythrocytes are small in size and poor in

hemoglobin and produce a hypochromic microcytic anemia of the type seen in conditions such as primary hypochromic anemia, nutritional anemia, chronic blood loss and hookworm disease (Wintrobe[16]), microcytic hypochromic anemia in infants and children (Faber et al.[17]) and certain nutritional anemias in infants and children (Josephs[18]). The anatomy of the red cell in chlorosis is well illustrated by a diagram suggested by Haden[19] showing a cross section view of the mean cell in various clinical conditions (figure 1).

Blood Platelets. The most striking hematologic finding in patients with chlorosis is the frequently encountered thrombocytosis which may be very

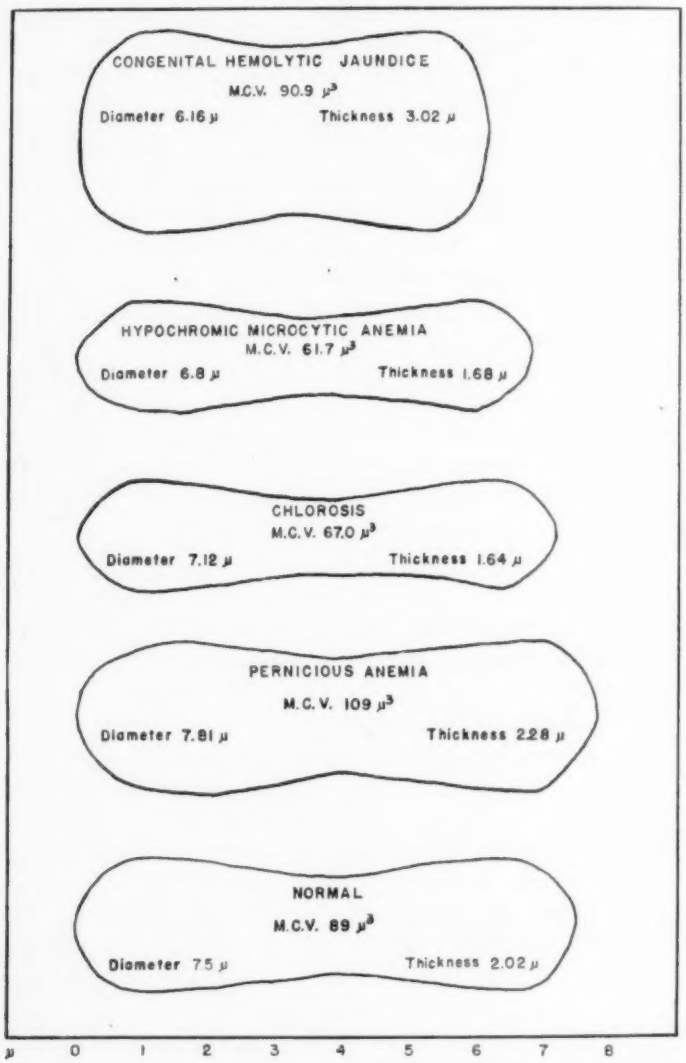

FIG. 1. Cross section and measurements of the erythrocytes in various clinical conditions.

marked (table 1, chart 2). According to the method described by me elsewhere [20] the platelets may be divided, according to size, into four groups: Group I, consisting of small platelets the diameter of which is one-quarter that of a red cell, or about 1.8 microns; group II, consisting of medium-sized platelets with a diameter one-third that of a red cell, or about 2.5 microns; group III, consisting of large-sized platelets with a diameter one-half that of a red cell or greater, or about 3.6 microns, and group IV, consisting of irregularly shaped platelets. The differential platelet formula of normal adults is usually as follows: Group I, about 19 per cent; group II, about 63 per cent; group III, about 17 per cent, and group IV, about 1 per cent. The small platelets, those belonging to group I, are the juvenile forms and have been shown by Barta,[21] Zeller,[22] Jürgens and Naumann [23] and Jürgens [24] to agglutinate very readily. The thrombocytosis in patients with chlorosis is characterized by the presence of numerous small platelets of group I. These juvenile, easily agglutinating platelets constitute a significant predisposing factor in the development of spontaneous venous thrombosis at times observed in this condition (in 2 to 3 per cent of cases, according to Cabot [25]). Chlorosis must be classed, therefore, as a definite thrombophilia along with conditions such as certain post-splenectomy states (Rosenthal [26]), postoperative states (Hueck [27]), fractures of long bones (Galloway [28]), parturition (Dawbarn, Earlam and Evans [29]), tuberculosis (Brock and Rake [30]), malignancy (Naegeli [2]), polycythemia vera (Jürgens and Bach [31]), severe acute hemorrhage (Jagić and Klima [32]) and post-infectious states. In all these conditions the tendency to the development of spontaneous venous thrombosis is always associated with an elevated platelet count. Essential thrombophilia recently described by Nygaard and Brown [33] seems to constitute an exception, for in this condition the platelet count is normal. The behavior of the total and differential platelet counts in chlorosis under iron therapy is totally different from the behavior of the thrombocytes in other types of anemia during treatment (chart 2).

There has been considerable diversity of opinion regarding the possible relationship between classical adolescent chlorosis, summarized recently by Patek and Heath,[1] and primary hypochromic anemia (called also idiopathic hypochromic anemia, simple achlorhydric anemia, cryptogenic achylic chloranemia, chronic chlorosis, hypochromic gastrogenous anemia) first clearly defined by Faber [34] and described more recently in detail by Witts,[35] Dameshek,[36] Minot [37] and Wintrobe and Beebe.[38] Thus Witts [3] is of the opinion that, in the absence of achlorhydria and dysphagia, the microcytic hypochromic anemia in middle-aged women is allied to adolescent chlorosis. Bloomfield [39] maintains that it is impossible to differentiate chlorosis from primary hypochromic anemia. It seems to me, however, that chlorosis is a definite disease entity, a view entertained by many observers, Minot [37] among others. It occurs in two forms, a severe one which is rather infrequent and a mild one which is, according to Davidson,[40] quite common. It presents a number of characteristic features differentiating it definitely from

primary hypochromic anemia, as shown in table 2. It must be admitted that atypical cases of both conditions are occasionally encountered which seem indistinguishable.

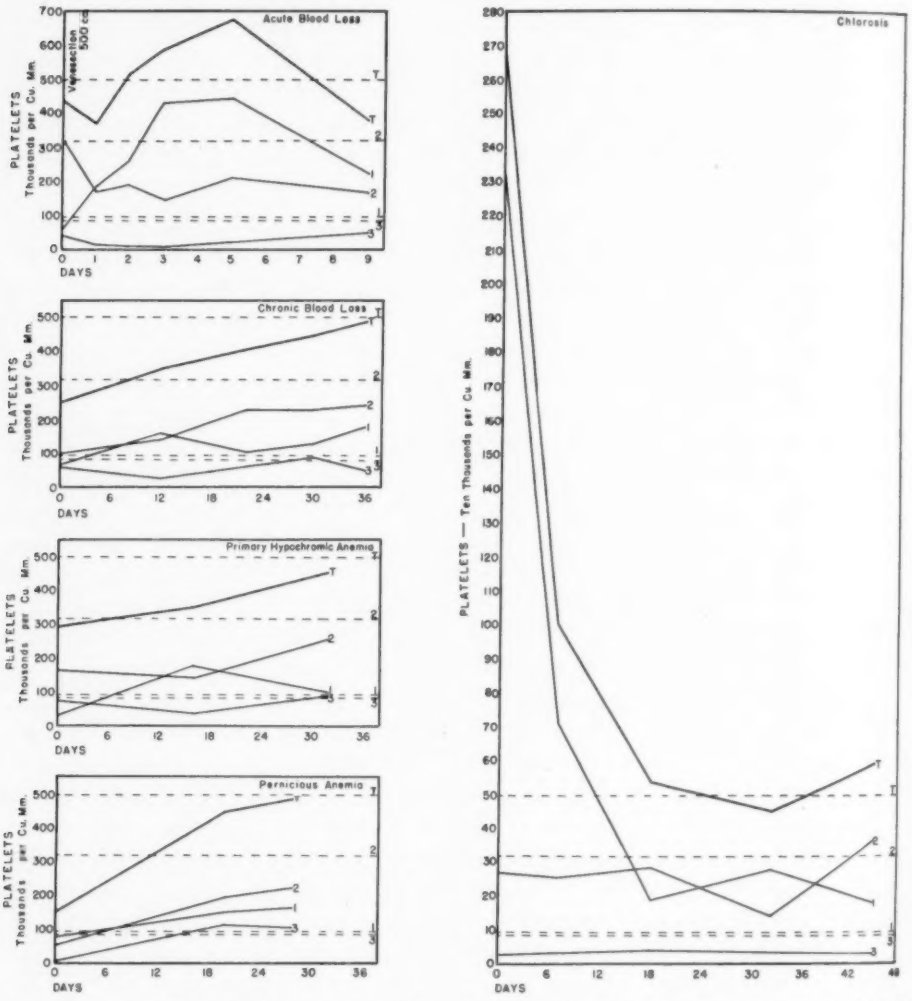

CHART 2. The behavior of the total and differential platelet counts in acute blood loss (venesection of 500 c.c. of blood on a normal adult who acted as donor for blood transfusion), chronic blood loss (chronic bleeding peptic ulcer), primary hypochromic anemia under iron therapy, pernicious anemia under liver therapy and chlorosis (case 1) under iron therapy. Dotted lines T represent the normal platelet levels, and dotted lines 1, 2 and 3, the normal absolute levels of the corresponding groups. Continuous lines T represent the behavior of the total platelet counts, and continuous lines 1, 2 and 3, that of the absolute counts of the corresponding groups.

SUMMARY AND CONCLUSIONS

Chlorosis, common a quarter of a century ago, has not disappeared. It is a definite clinical entity possessing characteristic features differing in

TABLE II

Differential Features Between Chlorosis and Primary Hypochromic Anemia

	Chlorosis	Primary Hypochromic Anemia
Age	14 to 20 years.	Usually fourth decade.
Sex	Limited to females.	Usually in females, occurs rarely in males.
Symptoms	Those of anemia.	In addition to those of anemia, frequently sore tongue, dysphagia (Plummer-Vinson syndrome), paresthesias, diarrhea.
Skin	Normal in appearance and texture; amount of pigmentation may be very scanty.	Often dry, inelastic; may present abnormal pigmentation.
Hair	Normal.	Frequently dry, prematurely gray.
Finger Nails	Usually normal.	Frequently brittle, grooved or spooned.
Tongue	Normal.	Frequently atrophic.
Splenomegaly	Rare (Naegeli[2]); slight splenomegaly in 10% of cases (Castle and Minot[41]).	Frequent (in 50% of cases (Witts[35])).
Gastric Secretion	Amount of free HCl may be increased, normal, reduced or absent.	Frequently post-histamine achlorhydria (in 60% of cases (Wintrobe and Beebe[38])).
Blood	Leukocytes: normal, often increased. Platelets: normal, frequently greatly increased.	Normal; frequently reduced. Usually reduced; occasionally normal (Dameshek[36, 42]).
Bone Marrow	Normal (Naegeli,[2] Grawitz[42]) or hyperplastic (Lee and Minot[44]).	Always shows normoblastic hyperplasia (Kaznelson, Weiner and Reimann,[45] Dameshek[46]).
Thrombophilia	In 2 to 3% of cases.	None.

many respects from primary hypochromic anemia. The most striking hematologic feature is the frequently encountered thrombocytosis which behaves in a characteristic manner under iron therapy. The thrombocytosis is characterized by the presence of numerous small, easily agglutinating platelets which create a condition predisposing to the development of spontaneous venous thrombosis and embolism.

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AN ARTICLE CONTRIBUTED TO AN ANNIVERSARY VOLUME IN HONOR OF DOCTOR JOSEPH HERSEY PRATT

THE LIFESPAN OF THE ERYTHROCYTES *

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IN anemia following bleeding or after the administration of phenylhydrazine, J. H. Pratt and P. Morawitz in 1908 noted an increase in the resistance of the erythrocytes. During the stage of advance of the anemia and during the first period of the restitution of the red cells, the limits of the maximal and minimal fragility were shifted in such a manner that erythrocytes less fragile than normal appeared and the most fragile erythrocytes disappeared. Pratt, in collaboration with S. Itami, continued these studies and found a considerable increase in the volume of the stroma of the erythrocytes during the phase of high resistance. This condition has been termed pachydermia of the erythrocytes by Morawitz.

In these studies Pratt touched the problem of the lifespan of the erythrocytes, our knowledge of which has not been advanced since. By counting the reticulocytes and analyzing the oxygen consumption of the erythrocytes, we can determine the presence of younger red cells in a manner approaching a quantitative measurement. By determining the osmotic fragility, which increases with age, we are able to get information on the age and the process of aging to which the erythrocytes are subjected. For this latter purpose we employ the method of L. Chanel, J. L. Hamburger, and I. Snapper which consists in determining the fragility by counting the number of erythrocytes undissolved in a series of concentrations of sodium sulphate solution.

In the organism, erythrocytes are destroyed by phagocytosis preceded by wear and tear, rather than by hemolysis. However, osmotic fragility indicates the aging process and can be taken as a quantitative measure, the units of which, namely, the concentrations, unfortunately cannot be related or transformed into units of time.

It is unknown whether the lifespan of the erythrocytes is shortened or lengthened in anemia. In the event that the lifespan of the erythrocytes is shortened, this shortening would contribute to the degree of the anemia; in the event that the lifespan is lengthened, this lengthening would compensate for the poor formation of the red cells.

In studying the osmotic fragility in anemic conditions, we rediscovered some findings made by Pratt and his co-workers. In anemia following hemorrhage, in pernicious anemia, and during the recovery period from these conditions, we found the least resistant groups of cells (i.e., oldest groups) absent, as indicated in the following protocols (tables 1, 2 and 3).

As shown in these illustrative examples, erythrocytes disappear before they approach the highest degree of osmotic fragility.

* Received for publication March 9, 1937.

TABLE I

Case of Duodenal Ulcer. Hemorrhage

% Na_2SO_4

Date	1.9	1.8	1.7	1.6	1.5	1.4	1.3	1.2	1.1	1.0	.9	.8	.7	Millions Erythrocytes per c.c.
IX. 11						14	29	63	76	96	99	100		2.4
IX. 15							21	42	67	88	95	98	100	1.9
IX. 18		4	12	23	27	23	50	63	77	87	96	100		2.4
IX. 30		4	7	10	39	57	68	84	97	99	99	100		4.6
IX. 10				30	35	39	58	79	99	99	100			4.7

TABLE II

Case of Pernicious Anemia. Treated With Liver Extract

% Na_2SO_4

Date	1.9	1.8	1.7	1.6	1.5	1.4	1.3	1.2	1.1	1.0	.9	.8	.7	Millions Erythrocytes per c.c.
III. 10					7	9	11	32	71	83	91	97	100	2.4
III. 11						3	7	27	46	66	91	95	100	1.9
IV. 24			2	18	31	38	53	65	83	91	100			4.6
V. 1			5	7	19	29	44	66	83	94	100			4.7

In anemia following hemorrhage there is no reason why destruction of erythrocytes should occur on a greater scale. From these observations it is evident that under the circumstances there is certainly no delay in the destruction of the erythrocytes and no prolongation of their existence. Therefore, it is reasonable to assume that the rate of destruction of the erythrocytes does not differ from the normal. Normally the daily production of erythrocytes equals the destruction (denominated as a), thus guaranteeing the constancy of their number. In any period of anemia in which restitution of the red count takes place, blood formation is increased up to about 100 per cent of the normal (i.e., to $2a$). If the average span of life of the erythrocytes is denominated as b, the whole number of the red cells is ab. Normally this figure is composed of groups of red cells equal in size but differing in age. When, by increased blood formation, the younger groups become larger ($2a$), the age groups are no longer equal. As blood destruction goes on at the same rate and each group is reduced equally by the hemorrhage, the oldest group is too small to cover the rate of destruction. Therefore, destruction must take place in the group next in age to the oldest

TABLE III

Rabbit. Experimental Anemia by Venesection

Date	2.2	2.1	2.0	1.9	1.8	1.7	1.6	1.5	1.4	1.3	1.2	1.1	1.0	0.9	Millions Erythrocytes per c.c.	Venous Puncture
5. VII		2	12	31	47	76	87	95	98	99	100				4.2	5, VII
6. VII			2	9	37	39	65	81	83	93	95	97	100		2.6	6, VII
7. VII						32	60	70	72	89	92	96	99	100	2.1	7, VII
8. VII						11	37	58	59	80	85	91	98	100	1.6	
9. VII						3	29	40	55	76	77	92	97	100	1.8	
11. VII					13	25	27	59	64	88	92	96	98	100	2.4	
13. VII				3	7	9	24	48	70	89	96	98	98	100	3.3	
15. VII		1	5	27	37	50	59	82	95	96	98	100			4.3	
17. VII			3	13	30	36	53	78	88	96	99	100			4.3	
20. VII			2	8	12	23	38	60	81	96	99	100			4.1	
23. VII			3	10	14	26	42	58	81	94	99	100			4.2	

group, and this process continues as long as the recently formed larger groups (*2a*) are aged down to the zone of destruction (table 4).

This may be demonstrated in the following table, in which, for the sake of better understanding, absolute figures are substituted for general figures and the age groups of erythrocytes reduced to 10.

TABLE IV

Formation and Destruction of Erythrocytes after Hemorrhage in 5-Day Periods

Age Groups	Before Hemorrhage		After Hemorrhage Days													
			5	10	15	20	25	30	35	40	45	50	55	60	65	70
1	.5	.3	1.	1.	1.	1.	.5	.5	.5	.5	.5	.5	.5	.5	.5	.5
2	.5	.3	.3	1.	1.	1.	1.	.5	.5	.5	.5	.5	.5	.5	.5	.5
3	.5	.3	.3	.3	1.	1.	1.	1.	.5	.5	.5	.5	.5	.5	.5	.5
4	.5	.3	.3	.3	.3	1.	1.	1.	1.	.5	.5	.5	.5	.5	.5	.5
5	.5	.3	.3	.3	.3	.3	1.	1.	1.	1.	.5	.5	.5	.5	.5	.5
6	.5	.3	.3	.3	.3	.3	.3	1.	1.	1.	1.	.5	.5	.5	.5	.5
7	.5	.3	.3	.3	.3	.3	.2	0	.5	1.	1.	1.	.5	.5	.5	.5
8	.5	.3	.3	.3	.3	.1	0	0	0	0	.5	1.	1.	.5	.5	.5
9	.5	.3	.3	.2	0	0	0	0	0	0	0	0	.5	1.	.5	.5
10	.5	.3	.1	0	0	0	0	0	0	0	0	0	0	0	.5	.5
Total	5.0	3.0	3.5	4.	4.5	5.	5.	5.	5.	5.	5.	5.	5.	5.	5.	5.

Discussion of Table IV:

1. Before hemorrhage, 5000 c.c. of blood are present. The blood count is 5 million per c.c. The whole blood holds 25×10^{12}, and 1 liter contains 5×10^{12} erythrocytes.

2. The erythrocytes are divided into 10 groups of different age. Before the bleeding each group holds 0.5×10^{12} erythrocytes per liter and after the bleeding, 0.3×10^{12}. The vertical columns show the composition of the blood in age groups during recovery. The lifespan of the erythrocytes is assumed as 50 days.

3. Normal formation and destruction of blood in 5 days $= 0.5 \times 10^{12}$.

The erythrocytes formed during the recovery from anemia are aging, as shown in the table marked by the dark lines. Thirty days after the hemorrhage, the blood contains 6 groups of red cells rather than 10 of different age, the older ones having disappeared. After the thirtieth day, the recently formed erythrocytes enter the zone of destruction.

As far as fragility is concerned, the findings in table 4 parallel the experimental findings demonstrated in table 3. While a restitution of the red blood count is finished within 20 days after hemorrhage, the restitution of the normal age groups of the red cells takes 70 days.

The absence of the red cell groups made up of older erythrocytes in anemic conditions can be understood from the character and the action of the red cells.

As the erythrocytes have no nuclei, no metabolism and no facilities for repair or for reproduction, they can hardly be considered as living cells. Their main constituent, hemoglobin, performs its function of binding and releasing oxygen in the same manner when separated from the corpuscle, simply as a chemical compound. The red cell is nothing more than a chemical machine and as such is subjected to wear and tear.

The stress on the erythrocytes is evidently due to their function. Binding and releasing oxygen is not only a chemical process, restricted to the quality of the hemoglobin, but concerns the red cell as a whole. By taking up CO_2 from the tissues into the blood, chlorides and water enter the erythrocytes in order to maintain the osmotic as well as the acid-base equilibrium. Thus the erythrocytes grow larger and assume a different shape. The opposite process takes place in the lungs. By this continuous process of hydration and dehydration, the stroma of the erythrocytes deteriorates. The deterioration is noticeable by the decrease in the size of the erythrocytes and by their increased fragility.

In anemic conditions a smaller amount of hemoglobin and a smaller number of erythrocytes have to carry the same amount of oxygen into the tissues. Regardless of whether the release of oxygen in the capillaries, i.e., the arterio-venous difference, is enlarged, or whether the erythrocytes are carried around more rapidly, the stress on the red cells is greater.

The particular items are as follows: 1 gm. hemoglobin at 0° and 760 mm. pressure binds 1.34 c.c. of oxygen (these figures are sufficient for comparison). Normally the blood contains 700 gm. of hemoglobin. Therefore, the arterial blood (350 gm. of hemoglobin) is capable of binding about 500 c.c. of oxygen. If the oxygen consumption in 24 hours is taken as 400 liters, and arterio-venous difference in oxygen saturation as 30 per cent, the erythrocytes have to act 2400 times in 24 hours in the double process of binding and releasing oxygen. In anemic conditions this figure increases corresponding to the deficit of hemoglobin. Thus erythrocytes are worn out faster. With the number of actions, the stroma of the erythrocytes undergoes a continuous alteration, which after a definite number of these actions results in a state of inertia. Every colloidal structure is subjected to this alteration, which, usually, is termed syneresis. Erythrocytes with an outworn stroma are unfit for the process of hydration and dehydration, less permeable for gases as well as for water and ions, and ready for destruction even before they approach the highest degree of osmotic fragility.

Thus it is evident that the lifespan of the erythrocytes cannot be measured in units of time, but only in number of actions. The smaller the number of the erythrocytes, the larger the oxygen consumption, the shorter the lifespan of the red cells.

The old and popular conception that by bodily exercise, outdoor life and high altitude blood is more rapidly renovated, is in complete harmony with these facts and their interpretation.

AN ARTICLE CONTRIBUTED TO AN ANNIVERSARY VOLUME IN HONOR OF DOCTOR JOSEPH HERSEY PRATT

THE MINNEAPOLIS GIANT *

By H. GRAY, *San Francisco, California*

GIANTS are not only dramatic to the layman as extreme variations of the human being, but valuable for the study of growth. In this respect they afford a considerable quantity of evidence which can profitably be analyzed in comparison with normal proportions, particularly of the extremities.

CASE REPORT

J. A., a single white male of 46 years, may be called the Minneapolis Giant, after his birthplace. He was admitted to Lane Hospital November 1, 1936, with the chief complaint of foot ulcers of four years' duration.

Family History. His father's father, the Norwegian Giant, was reputed to be 2520 mm. in height (8 ft. 4 in.), while the father's own height was variously stated by the patient as 2286 mm. (7 ft. 6 in.) and 1930 mm. (6 ft. 4 in.), and the mother as 1880 mm. (6 ft. 2 in.); there was one sister of normal size. The father died at 41 years of pneumonia, the mother at 32 also of pneumonia; the sister is alive.

Residential History. Born in Minneapolis in 1890, he left there at two years for North Dakota, and at nine years started traveling in shows, all over the United States, and, according to his story, to Hawaii 14 times, to China several times, Australia twice, Europe twice, South America once. He has made Los Angeles and San Francisco his home for 13 years.

Occupation. Carnivals, circuses, movies, shows, vaudeville, so many that he cannot remember the names of any except Harold Lloyd's "Why Worry?" in 1923, in the advertising for which he was claimed to be the second tallest man in the world. This claim would seem to indicate insufficient information about other living giants, which information, to be sure, is hard to get. For four years he has been unfit to work because of the ulcers on his feet.

Habits. Very irregular. His sleep has been irregular and lately troubled with insomnia. Exercise has been minimal during the last four years because of the ulcers on his feet, so that he has spent most of his time sitting around. Drugs in any form are denied. Alcohol he drinks only occasionally and has never been an habitual drinker, though on October 30, 1936, he was arrested by eight policemen because he acted a little peculiarly, having consumed by his account "maybe five or six cases of whiskey." In jail his breakfast, according to the lieutenant, consisted of two gallons of coffee, and he admits being an inveterate coffee drinker, sometimes making it his entire meal and taking eight cups a day. Tea does not interest him. Also he is an habitual smoker. Lately he has been taking patent tonics to "build up his blood." His diet has been inadequate during the past four years.

Medical History. Diseases, injuries, operations: nothing significant. Questioned by systems, the points of possible interest may be reduced to the following:

Head: No trauma, frontal headaches once a month during second period of growth at 28; for 15 years noticed that he had to turn his head in order to see toward the outer sides; and this bi-temporal hemianopsia kept creeping inward until about

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five years ago both lateral halves of his fields of vision were almost gone; no progression since.

Ears, nose, throat, lungs: all negative. Teeth: all removed 8 years ago. Hair: on face and body always very scanty. Heart: slight dyspnea. G. I.: appetite always good but never Gargantuan. Constipated for years. G. U.: Nocturia three times, for years, attributed to drinking a gallon of fluid a day. Venereal denied. No libido ever. Muscular strength: never remarkable. Nervous system: education

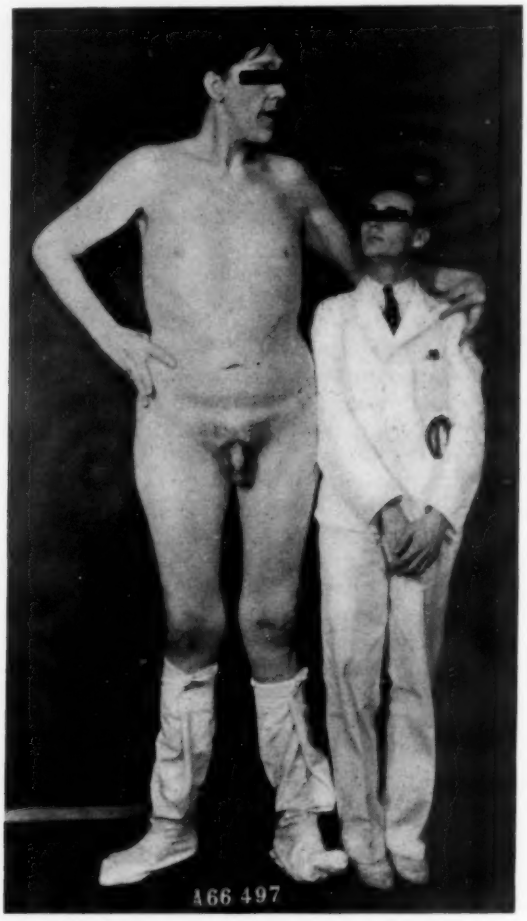

FIG. 1. The Minneapolis giant, 2134 mm. (7 ft. 0 in.) beside Dr. J. S. M., 1763 mm. (5 ft. 9½ in. net).

ceased at second year of high school; and subsequent learning has been difficult because of poor memory, especially of recent years. His disposition he regards as nervous but good, except during 24 hours after attacks. These will now be described.

About five years ago, say in 1931, he had his first epileptic fit; he was very tired when he went to sleep and during his sleep he thinks he had an attack because when he woke up his tongue was sore. His first attack in public was about four years ago when he was standing on a corner waiting for a street car; his body became stiff, teeth ground and he became unconscious for about five minutes, after which he felt

weak and slept for some time. The spells have occurred at intervals varying from two weeks to six months. The latest attack was two weeks before admission; he was sitting in a chair when he slumped over suddenly and fell to the floor unconscious; afterwards he was told that his legs had become rigid and then started quivering. His teeth grind and he thinks he bites his tongue. Never other injury. Never incontinent. He feels sleepy and depressed afterwards.

Olfactory hallucinations, an odor like hard-boiled eggs freshly opened, have been common since the grand mal began. Such uncinate attacks occur in 7 per cent of acromegalics (Davidoff [1]).

Enlargement of hands, feet, jaw and lip he first noticed about 1921 at the age of 31, about five years after acromegaly was recognized at the Mayo Clinic. This extraordinary delay in a patient's appreciation of acral enlargement has previously been recorded by Buday and Jancso [2] (1894) and by Mark [3] in his book on his own case.

Weakness began about the time of his second growth at 28, and has become worse in the last five years.

Ulcers began on his feet about 4 years ago. The first was on his right foot, apparently due to an inflammation under a callus; it cleared up. On his left foot the ulcer began about 18 months ago. He has been using crutches or a cane off and on for the last four years. Also there has been a fissure on his upper lip for the last five years, which has refused to heal, and which he attributes to repeated trauma from playing his harmonica.

Weight and Growth History. This is shown in table 1.

TABLE I

Growth History

Date	Age	Stature Net		Weight Net		Observer
		mm.	ft.-in.	kg.	lbs.	
Mar. 5, 1890	Birth	Unknown		Unknown		
1898	8	1929	6-0	"gangly"		Patient
		Began Spurt I				
1908	18	2134	7-0	Unknown		Patient
1915	25			127.0	280	Patient
Nov. 23, 1916	26.7	Not stated; acromegalic; genit. infant., bi-temp. hemianop., sella enlgd.		151.5	334	Mayo Cl.
1918	28	Began Spurt II				Patient
1921	31	He first noticed enl. extrs., jaw, and lip		228.2	503	Patient
1923	33	2438	8-0	210.9	465	Patient
1930	40	He noticed loss wt., strength, color		181.4	400	Patient
1931	41	First grand mal				Patient
Mar. 7, 1933	43	2154	7-1	136.4	300	San Francisco Hospital
Nov. 2, 1936	46.7	2362	7-9	129.3	285	Patient
		2134	7-0	122.0	268	Gray
Nov. 9, 1936	46.7			125.4	276	Gray

Physical Examination. A veritable giant and obviously acromegalic. Mandible very long and large but protrudes only slightly. Maxillae very prominent as are the supra-orbital ridges. Lips thick. Voice is not deep nor loud but weak. Ears large.

Skin quite pale, somewhat tawny, is coarse but pliable with many wrinkles; it is loose and he has evidently lost weight.

Eyes: Pupils and movements normal without nystagmus; wears glasses.

Fundi: Generally pale. Veins not especially full. No sclerosis of vessels. Both discs on medial halves are almost obliterated with irregular, poorly marginated portion remaining. Both discs in outer halves are pale yellow-white, more marked on left, appearance of optic atrophy.

Ears: Externally negative. Watch heard, both sides, 25 cm. vs. normal 30.

Nose: Septum moderately deviated to right; no discharge.

Teeth: Out. Oral mucous membranes moderately pale.

Fig. 2.

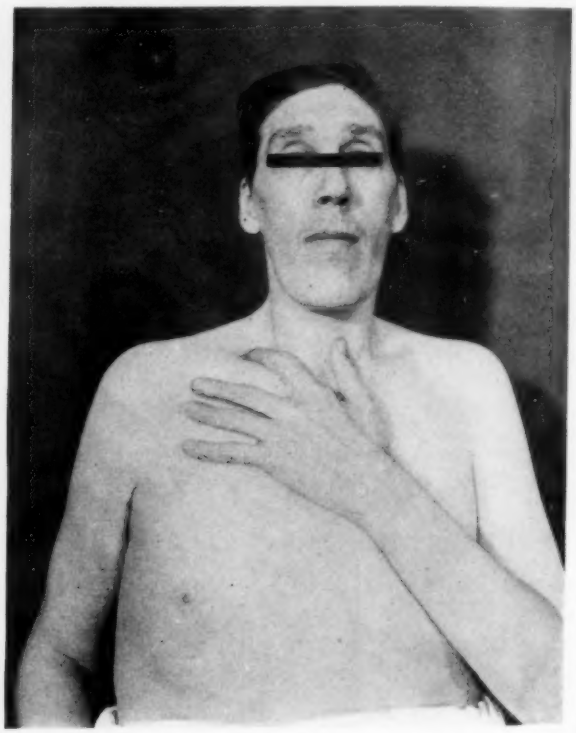

Fig. 3.

FIG. 2. Showing extraordinary claw toes and his characteristic posture and expression.
FIG. 3. Close-up of face and hand.

Tongue: Slightly large; no papillary atrophy.

Tonsils, throat, neck, thyroid, heart, peripheral vessels, lungs, abdomen: all negative.

Pulse: 54–84. Blood pressure 110 mm. mercury systolic and 70 diastolic.

Hair: On scalp it is dark brown with some gray; fine in texture, normal in amount. Brows and lashes normal. On face only slight down; last shaved 5 months ago. In axilla very thin and silky. On chest none. Crines scanty with horizontal upper edge. On arms none. On lower legs slight fuzz.

Genitalia: Penis small, about 5 cm. long; infantile. Testes small, soft; about 2 cm. long.

Rectal: Sphincter tone poor; patient complains of great pain in rectum.

Prostate: Can hardly be felt.

Spine: No kyphosis, scoliosis, nor lordosis.

Extremities: Bony with wasted flabby soft parts. Hands and feet large, only moderately large in proportion to rest of extremities. Single penetrating ulcer on bottom left foot. (J. D. Myers.)

Urine: Acid, 1.010, no albumin, no sugar, no blood, casts or pus.

Blood: Wassermann negative, RBC 4.57 million, Hgb. 70 per cent, WBC 11,100, neutrophiles 68 per cent, eosinophiles 5 per cent, basophiles 1 per cent, lymphocytes 22 per cent, monocytes 4 per cent; and a few days later RBC 4.38, Hgb. 68 per cent, WBC 12,350, neutrophiles 68 per cent, eosinophiles 1 per cent, basophiles 0, lymphocytes 28 per cent, monocytes 3 per cent. Sugar tolerance: Fasting blood sugar 120; ½ hr. 160; 1 hr. 165; 2 hrs. 140 mg. per 100 c.c.; cholesterol 117, urea 27, chlorides as NaCl 435. Van den Bergh direct negative, indirect 0.55 units; icterus index 4.3.

Stool: Negative.

Basal Metabolic Rate: Minus 17 per cent; pulse 60–58. Another day minus 11.

Electrocardiogram: Sinus rhythm; rate 60; P.R. 0.17; QRS 0.08 sec.; left axis deviation.

Vital Capacity: 6.1 liters.

Shoes: The heels on his shoes are 56 mm. (2.2 in.), and their weight is 3.2 kg. (7 lbs.).

Roentgen-Ray: A film record was made of this gigantic skeleton. The cranium is not enlarged, but its thickness is unusually great, the calvarium measuring nearly 2 cm. in most places. The jaws are edentulous, the mandible very long. The sella is large, measuring about 2 cm. backward, and is pretty deep; neither the floor nor the dorsum appear to be suffering from pressure atrophy; the anterior clinoids appear intact, although their structure is not very dense.

In the infected left foot no roentgen evidence of osteomyelitis is detected; the right second and third metatarsals have been broken and the second is ununited with dorsal lateral displacement of the toe; this evidently happened a very long time ago.

The phalangeal tufts of the big toes are quite unusual in form (figure 4) while in the other toes there is only a slight unevenness of the development of the tufts. The tufting of the fingers is distinctly less than average (figure 5).

The heart is well within normal limits for a man of this size.

The lungs show some infiltration in both upper lobes, on the right in the second interspace and on the left in the apex and first and second interspaces. Also in the first and second interspaces are small areas which look like cavities but may be emphysematous blebs. At any rate we have evidence of old tuberculosis in each upper lobe. (R. R. Newell.)

Eye Consultation: O.D. 20/70, O.S. 20/25. Fundi: discs markedly pale, vessels and maculae normal. Fields: bi-temporal hemianopsia; the field cut comes very close, up to about 2° to the macula on the right and to about 5° on the left. (M. Miller.)

Orthopedic Consultation: Clawing toes. Marked prolapse of heads of metatarsals, especially left foot. Chronic ulceration on sole without underlying osteomyelitis. Some sensory disturbance. Plates seem to be satisfactory. Ulcer will probably heal with bedrest and elevation. (D. S. King.)

Neurological Consultation: Tall individual with acromegalic features. Generalized weakness but no paralysis. No deep reflexes elicited. No pathological reflexes. All modalities of sensation intact except over feet and ankles where there is a marked hypesthesia and hypalgesia. Muscle position sense in toes fair. Cranial nerves: Bi-temporal hemianopsia grossly. Discs pale. Balance of cranials intact. Psychologically he is generally coöperative but quite easily irritated especially if obstructed in any way. Manner effeminate and some of reactions quite juvenile and immature. Sensorium intact. I.Q. is 88 which is dull normal. Some scatter shown indicative probably of organic deterioration. Patient has expressed suicidal ideas which make

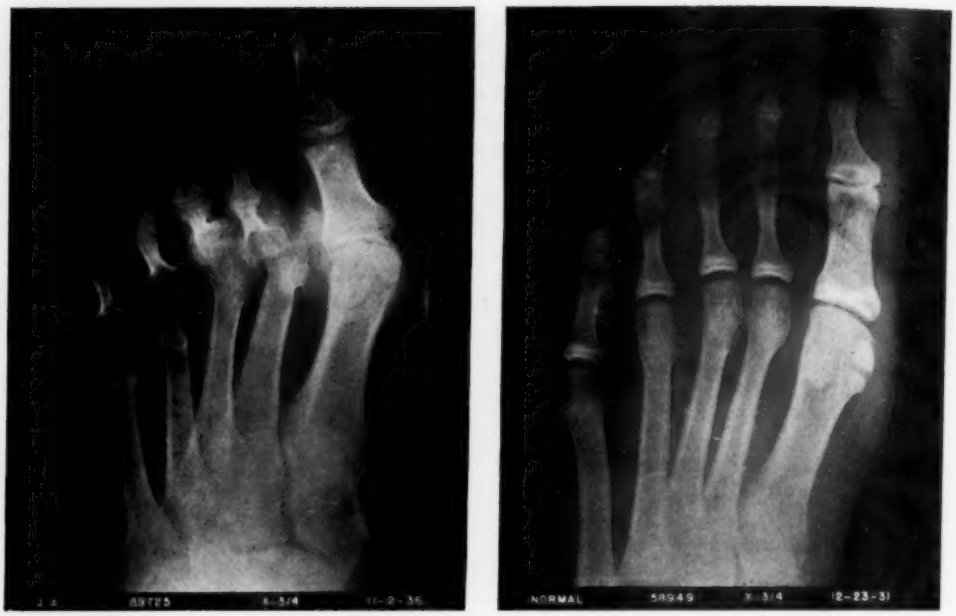

FIG. 4. X-ray of foot of patient and of normal, which in this cut is raised to approximately equal magnification for clearer comparison of unusual bony structure.

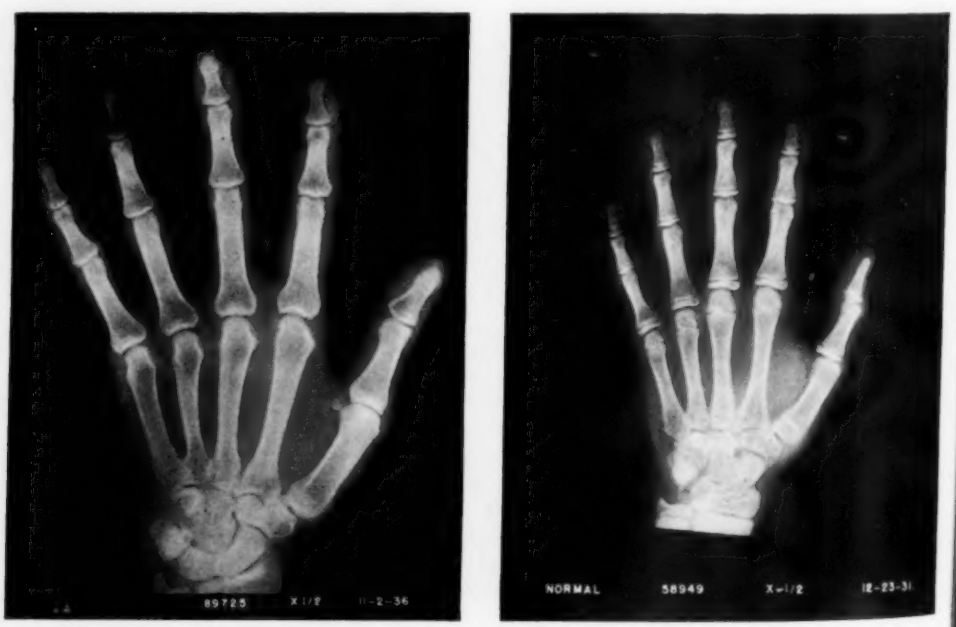

FIG. 5. X-ray of hand of patient and of normal, showing relative size and absence of traditional tufting.

prolonged hospitalization a consideration. Impression: 1. Pituitary adenoma with gigantism and acromegaly, destruction now resulting in hypofunction; 2. Epilepsy, symptomatic. (J. F. Card.)

Note by Visiting Physician (Nov. 2, 1936): The patient is immensely tall, looks somewhat tired and worn and has clearly lost much weight. Face has definite but moderate acromegalic appearance with thickening of supraorbital ridges and elongation of jaw. Tongue is large. Two plates. Consistency of skin is thin and smooth. There is transverse pubic hair of feminine type, moderate axillary hair, beard practically absent. Considerable deposition of fat about hips. Testes about 2 cm. in length and infantile, penis not obviously abnormal. Complete absence always of libido and potentia. Heart is fairly large, slow, sounds clear. Blood pressure rather low. No viscera felt in abdomen. There is definite bi-temporal hemianopsia with hand test. There is definite grayness of optic discs on both sides. Definite impairment of superficial sensation on feet. Knee jerks not obtained in bed. Definite deformity of feet which he thinks due to high heels. Small penetrating ulcer on ball of left great toe, probably connected with this also. Cranial nerves other than optic seem intact. Impression: The sequence of events here seems very clear: 1. hyperfunction of alpha cells of anterior lobe, beginning early in life with simple gigantism. There has probably been from the start a tumor which has destroyed or inhibited gonad-stimulating cells of pituitary, hence failure of sexual development, feminine habitus, lack of hair, etc. 2. The tumor after a period of more or less arrest evidently began to grow again causing acromegaly and pressure on chiasm with optic atrophy and bi-temporal hemianopsia. Secondary effects of long-standing acromegaly in form of weakness, anemia, etc., are explainable. (A. L. Bloomfield.)

Note on Epileptic Attacks on Ward (Nov. 2, 1936): Yesterday afternoon at 4:30 the patient had an epileptic attack; he gave a cry, and was discovered in a generalized clonic convulsion, unconscious, with much grinding of the jaws. Unconscious about five minutes, then lost abnormal movements, mentally confused for a few minutes, and fell into deep sleep. This morning feels well except "washed out" (J. D. Myers). Similar attacks at 10:30 a.m., Nov. 11; 11 a.m. and 12:15 p.m., Nov. 13, 1936, but lasting only about half a minute.

Diagnoses: Giantism due to hereditary hyperprepituitarism
Acromegaly
Hypoprepituitarism secondary to acidophile adenoma
Hypogonadism
Hypothyroidism
Low I.Q.
Epilepsy
Uncinate attacks
Anemia, secondary
Ulcer of foot
Claw toes
Barbed-arrow phalanges
Tuberculosis, inactive

Treatment: The diet was made as ample as the patient would eat and was found to vary from 4000 to 5500 calories; an average day's distribution was C 410, P 140, F 320, calories 5080. Iron was given as ferric ammonium citrate 50 per cent solution, 4 c.c. t.i.d.p.c. Liver and stomach concentrate was administered in the form of Extralin (Lilly & Co.) capsules, each 0.5 gram, 2 t.i.d.a.c., which for the 24 hours is equivalent to 120 grams of fresh liver. Adrenal cortex extract seemed indicated, but before any was obtained the patient left the hospital on Nov. 14. Thyroid extract (Armour & Co.) 0.13 gram daily, was begun on Nov. 7, and after four days the patient stated that his feet felt warm and sensitive for the first time in years.

Limitation of the activity of the eosinophilic cells of the anterior pituitary by operation was proposed to Dr. F. L. Reichert, but it was agreed to postpone surgical treatment until the general vigor could be improved. Radiation likewise was deferred, owing to the probability that the patient would leave town shortly so that follow-up would be inadequate.

After-History: Jan. 15, 1937, committed to Mendocino State Hospital.

Study of Build

Anatomical Measurements: The build of this giant with acromegaly and hypogonadism (often called by the ambiguous term infantilism) may be documented by the following figures and tables. Although eager for relief the patient was, like most giants, resistant to tests in general and measurements in particular; after meals and gifts of tobacco he became slightly less suspicious, and after the ego had been elevated by lavish deference, could finally be coaxed into transient assent. Comparisons of his build with normals may conveniently be treated under four main headings; stature, general set of anthropological measurements, extremities, and miscellaneous measurements.

Stature Comparisons: Humberd [4] (1936) had "never been able to find an absolutely reliable account of a human being who has ever attained as much as 8 feet (244 cm.) in height." Although he has tilted so persuasively at some reported data, as have others before him, there remain a number of undisputed taller giants (table 2).

Table II

The Taller Giants

Gallatin Giant	Lackey [5] 1899	2591 mm.
Irish Giant in Trinity College, Dublin	Cunningham [6] 1891	2590 mm.
Alton Giant Wadlow	Barr personal commun. 1936; this suggests that he had developed some kyphosis when seen by Humberd in 1937.[7]	2559 mm.
Austrian Giant	Topinard [8] 1885	2550 mm.
Giantess Wehde	Ranke, cited by Launois and Roy [9]	2550 mm.
St. Petersburg Giant skeleton	Cushing [10] 1912	2540 mm.
Kalmuck Giant in Orfila Museum, Paris	Topinard 1885	2530 mm.
Alton Giant Wadlow	Humberd [7] 1937	2521 mm.
Giant Byrne, or O'Brien	John Hunter, cited by Cunningham [6]	2490 mm.
Giant Wilkins	Dana [11] 1893	2450 mm.
Minneapolis Giant, the present case		2134 mm.

General Anthropological Comparisons. The giant's data are shown in table 3, columns 1 to 3. When we look for control series of measurements on tall, American born, normal, white men we find in no one place any set of dimensions complete. For the set used in our general routine study of build we chose the averages on the tallest group, namely 109 football

TABLE III

Anatomical Measurements, Routine, Metric and without Clothing

Measurement		Giant	Football Players		Coef. G/FB	Dev./SD	Expected Frequency
(1)	(2)	(3)	Mean (4)	SD (5)	(6)	(7)	(8)
Weight in kg.	W	122.0	77.3	9.3	1.58	4.8	$0.8/10^6$
Stature in mm.	S	2134	1780	74.0	1.20	4.8	$0.8/10^6$
Sitting height	Si	1090	929	33.9	1.17	4.7	$1.3/10^6$
Chest circumf.	C	1170	925	54.5	1.26	4.5	$3/10^6$
transv.	T	394	304	18.1	1.30	5.0	$0.3/10^6$
ant. post.	AP	260	228	15.4	1.14	2.1	18/1000
module	ChM	327	268	15.0	1.22	3.9	$48/10^6$
Shoulder bi-acr.	BA	472	394	20.7	1.20	3.8	$72/10^6$
Pelvis bi-crist.	BC	408	292	13.3	1.40	8.7	$1.6/10^{18}$
Head length	L	216	199	7.0	1.09	2.4	8/1000
breadth	B	164	156	4.8	1.05	1.7	
height	OH	138	135	5.1	1.02	.6	
module	CM	173	163	3.9	1.06	2.6	5/1000
Face height	MN	160	127	5.5	1.26	6.0	$.001/10^6$
breadth	BZ	160	142	5.0	1.13	3.6	0.2/1000
module	FM	160	134	4.1	1.19	6.3	
Nose height	NH	72	57	3.9	1.26	3.8	$72/10^6$
breadth	NB	38	36	2.2	1.06	.9	
	W/S	57.2	43.3	4.9	1.32	2.7	3/1000
	Si/S	51.1	52.1	1.1	.98	− .9	
	C/S	54.8	52.1	3.4	1.05	.8	
	T/S	18.5	17.2	1.1	1.08	1.2	
	AP/S	12.2	12.8	1.0	.95	− .6	
	ChM/S	15.3	15.0	.9	1.02	.3	
	BA/S	22.1	22.1	1.1	1.00	0	
	BC/S	19.1	16.4	.7	1.16	3.9	$48/10^6$
Above items in per cent of stature	L/S	10.1	11.2	.4	.90	−2.8	3/1000
	B/S	7.7	8.7	.4	.89	−2.5	6/1000
	OH/S	6.5	7.6	.3	.86	−3.7	.1/1000
	CM/S	8.1	9.2	.3	.88	−3.7	
	MN/S	7.5	7.1	.4	1.06	1.0	
	BZ/S	7.5	7.9	.4	.95	−1.0	
	FM/S	7.5	7.5	.3	1.00	0	
	NH/S	3.4	3.1	.2	1.10	1.5	
	NB/S	1.8	2.0	.1	.90	−2.0	
Index chest	AP/T	66.0	74.2	4.9	.89	−1.7	
trunk breadth	BC/BA	86.4	74.3	4.1	1.16	3.0	1/1000
cephalic	B/L	75.9	78.3	3.5	.97	− .7	
facial	MN/BZ	100.0	89.9	4.8	1.11	2.1	18/1000
face/head L	MN/L	74.1	63.9	3.3	1.16	3.1	1/1000
face/head B	BZ/B	97.6	90.9	2.7	1.07	2.5	6/1000
nasal	NB/NH	52.8	64.6	6.1	.82	1.9	

players whose average height was 1780 mm. (70.1 inches). Since these appeared in a publication inaccessible in many medical libraries,[12] the essential averages and standard deviations are reprinted in columns 4 to 5. A coefficient is calculated in the next column, (6), by dividing the giant by the normal; for example, the coefficient for stature shows that the giant is 20 per cent above the normal. Another method, more elaborate, but more refined, is to take the deviation of giant from the control and divide this by

the standard deviation (Dev./SD) as done in column 7; and to interpret this for the significant results, I have shown in column 8 how small a proportion of the population may be expected to show such extreme values; that is, if the distribution of giants follows the normal Gaussian law. Apparently it does not. Taking stature for an instance, the probability expected is seen to be 0.000,000,79, say, 0.000,001; hence in the United States with a population of over a hundred million people we should have more than 100 men as big as the Minneapolis giant; and certainly no such number has become known.

Extremities Comparisons: Acromegaly. In assessing the presence or absence of acromegaly, clinical practice might be made more objective by measurements aimed to determine whether the size of the organ, either absolutely, or better relatively to stature, is remarkable compared to that usual in normals. In the literature are scattered lengths and circumferences of such parts of the frame as happened to look extraordinary, usually without adducing control values from the literature or—when such do not exist, as is the case for many of the measurements taken—without supplying a single control. Clinical anatomy requires comparisons.

For the jaw, which it is true is hard to measure, the data are scantiest, and then by methods which are hard to apply in the living. By the method which is best to my mind, the radial distance from the earhole to the tip of the chin, what may be termed the chin radius or porion-menton, all that I can find are the following:

	mm.	/S	Giant/Norm
Normal 1820 mm. (71.7 in.)	128	7.03	
Minnesota Giant	155	7.26	1.21 = 21% excess
S.B. of Buday and Jancso [3]	180	9.09	1.41 = 41% "
R.S. of Pentagna [13] 1932 (child 11 yrs.)	120	9.09	

Foot length will be treated briefly since (1) so much more material is available for the hand, and (2) our giant's foot, while of course large absolutely, is when referred to stature (FL/S) actually smaller than normal.

	mm.	/S	Coef. Giant/Norm
Minnesota Giant	306	14.3	1.17 absolutely
245 Old Americans of Hrdlicka [14] (1925) of average stature 1744 mm.	261	15.0	.95 relatively

Hand Size. Methods have been exhaustively detailed by Bayer and Gray,[15, 16] 1933 and 1936. In the present connection the most illuminating ideas are suggested by considering hand length referred to stature (100 HL/S). Since this relationship is smaller the taller the person, the ratio is plotted against stature in figure 6. Normal means (maltese crosses) for

increasing heights according to Bach [17] have been spotted and a line fitted by eye to show the general trend. The variability of individuals is indicated by plotting 16 white males (simple crosses) (unpublished data). The Minnesota Giant is located (solid black spot). Other giants from the literature have been collected (open circles); these may be considered under several heads.

The extraordinary Alton Giant (double circles) [7] is seen at three ages—12, 13, and 18 years. Clearly he was first a simple giant and later developed acromegaly.

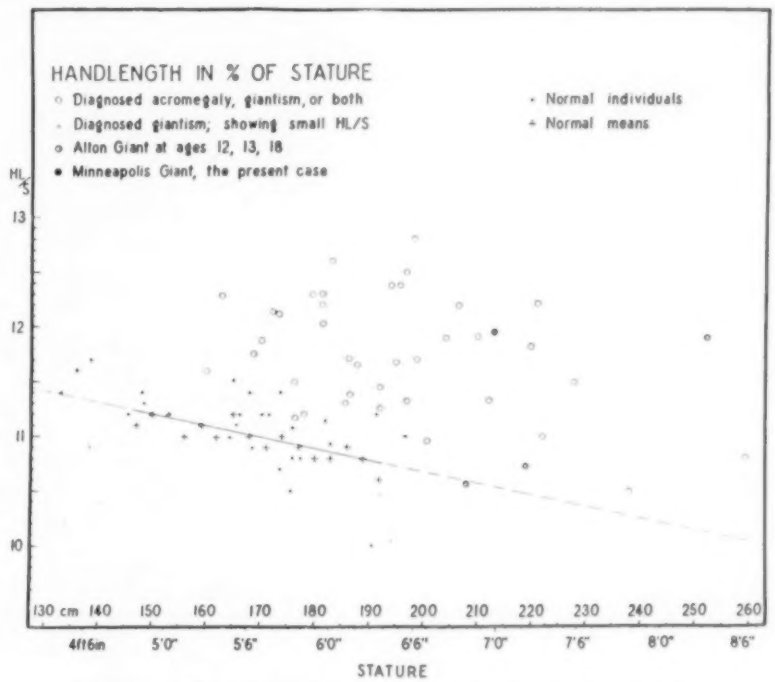

FIG. 6. Relative hand-length (HL/S) plotted against stature.

A paradoxical group is next noticed: diagnosed giants and revealing ratios actually smaller than normal (small circles). Out of 45 giants there were 5 such, or 11 per cent. Incidentally the two juvenile giants bore the additional diagnosis of precocious puberty. Listing them in order of increasing stature we get table 4.

A group with such incredibly large values for this ratio HL/S that they would lie far above the nearest point on the diagram (therefore not inserted) are:

		S	HL/S
R. S.	Pentagna 1932	1320	13.6
F. V.	Pel [18] 1906	1720	18.3

TABLE IV
Giants with Paradoxically Small Hands (HL/S)

		S	HL/S
K. K., aged 8	Linser [19] 1903	1380	10.9
C. H., aged 6	Hudovernig and Popovits [20] 1903	1400	10.4
Würzburg Giant	Bassoe [21] 1922	1920	10.5
P. C.	Bonardi [22] 1899	1940	10.1
American Giant	Hinsdale [23] 1898	2286	10.9

The main group consists of persons diagnosed giantism, acromegaly, or both (larger circles); their locations warrant the important conclusion that 89 per cent of giants are in fact acromegalic.

Hand Proportions in Detail. A more refined comparison, partly as a

TABLE V
Anatomical Measurements of the Hand

Measurement (1)	(2)	Giant (3)	16 Normals Mean (4)	Coef. (5)
Ray I	I	183	140	1.31
Ray II	II	247	184	1.34
Ray III	HL	255	192	1.33
Ray IV	IV	246	182	1.35
Ray V	V	222	158	1.41
Midfinger length	FL	134	96	1.40
Palm length	PL	121	96	1.26
Hand breadth	HB	114	86	1.33
Bi-styloid br.	Bs	78	59	1.32
Hand circumf.	HC	251	210	1.20
Palm circumf.	PC	254	219	1.16
Wrist circumf.	Wr.	195	167	1.17
Above items in per cent of stature	I/S	8.6	8.0	1.08
	II/S	11.6	10.6	1.09
	HL/S	11.9	11.1	1.07
	IV/S	11.5	10.5	1.10
	V/S	10.4	9.1	1.14
	FL/S	6.3	5.5	1.15
	PL/S	5.7	5.5	1.04
	HB/S	5.3	5.0	1.06
	Bs/S	3.2	3.4	.94
	HC/S	11.8	11.9	.99
	PC/S	11.9	12.5	.95
	Wr/S	9.1	9.6	.95
Above items in per cent of hand length	I/HL	71.8	72.7	.99
	II/HL	96.9	95.9	1.01
	IV/HL	96.5	94.6	1.02
	V/HL	87.1	82.3	1.06
	FL/HL	52.6	50.0	1.05
	PL/HL	47.5	49.9	.95
	HB/HL	44.7	45.0	.99
	Bs/HL	27.1	29.8	.91
	HC/HL	98.4	105.4	.93
	PC/HL	99.6	114.4	.87
	Wr/HL	76.5	85.3	.90

matter of record, partly as a matter of method, can be given, based on 16 normal white males, for most of the measurements, though on only 7 of them for the items Bs, HC, PC, Wr. The principal conclusions are these: In absolute measurements the giant is over 30 per cent larger than the average for this particular sample of 16 normals. The measurements related to stature make allowance for the greater stature of our subject and are therefore more useful; they are given in the second panel of the table. They show that the giant's hand is larger relatively to his size than is the case with normals, with the exceptions that the circumferences of hand and wrist are smaller relative to height than is the case with normals. An acromegalic with the broad type of hand would perhaps yield circumferences relatively larger than normal. The measurements related to the size of the hand, as judged by the length of the central ray or hand length, is given in the third panel of the table; the index, ring, and little finger rays are all more nearly the length of the midfinger ray than is the case in normals; the thumb ray, however, is abnormally short. The data are in table 5.

Miscellaneous Comparisons. For the miscellaneous items put on record in table 6 satisfactory controls have not been found. In order not to extend

TABLE VI

Miscellaneous Measurements

		mm.	/S
Head			
Circumf.		620	29.1
Ear			
Length	EL	77	3.6
Breadth	EB	37	1.7
Lip			
Slit		57	2.7
Thickness		16	0.8
Span	Sp	2190	102.6
Lower Length sym-sole	LL	1140	53.4
Upper Length v-sym	UL	994	46.6
Arm			
Upper	ac-r	411	19.3
Lower	r-sty	334	15.7
Leg			
Upper length	tro-ti	720	33.7
" breadth	bi-cond	136	6.4
Lower length	ti-sph	460	21.6
" breadth	bi-mal	87	4.1
Foot			
Length	FL	306	14.3
Breadth	FB	110	5.2

comparisons tediously, they may be ended with an examination of the relative growth of the three segments of the upper extremity—upper arm, lower arm, and hand length. In the present giant the overgrowth is least marked in proximal segment, next in the forearm, and most in the distal segment, the hand. The analysis is given in table 7, in which as controls (column 4) I have copied the dimensions for the tallest group, stature 1920

TABLE VII

Relative Overgrowth of the Several Segments of the Arm

Segment	Giant		Normal		
(1)	mm. (2)	% of Total (3)	mm. (4)	% of Total (5)	Coef. (6)
Upper	411	41.1	373	43.7	0.94
Lower	334	33.4	277	32.5	102.8
Hand	255	25.5	203	23.8	107.1
Total	1000	100.0	853	100.0	

mm., in Bach's table; then I have figured each segment as a percentage of the total extremity (columns 3 and 5), and finally divided the giant by the normal (last column), with striking emphasis stated, namely, the more distal the segment, the greater the degree of overgrowth.

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ORGANIC DISEASE OBSCURED BY NEUROTIC BEHAVIOR *

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The frequency of neurotic behavior in patients seen in general medical practice, the difficulties met in making accurate diagnoses and in caring for such patients, the present interest of physicians and surgeons in this subject as shown by their writings and discussions, and the increasing number of patients labelled " neurotic," emphasize the importance of critical evaluation of emotional states in the sick.

Symptoms of neurotic origin simulating true organic disease, but without demonstrable lesion, are common. Neurotic behavior, however, may follow or be intensified by organic disease, or such behavior may exist in the presence of organic lesions, in an apparently unrelated way. The patient is a total personality, and responds to intrinsic as well as extrinsic factors. It is therefore of great importance that we constantly remain aware of the possibility that symptoms may precede for months, even years, the discovery of a slowly developing organic lesion, screened and obscured effectively by neurotic behavior, as is demonstrated in the following reports:

Case 1. An unmarried Jewess, 38 years old, complained of inability to walk. Fifteen years ago she had attacks during which she would scream, jump, stamp her feet, and become otherwise uncontrollable. She had always shown great pride, independence, jealousy, sensitiveness, explosive outbursts of temper, and a strong love of children. She had had an appendectomy, a right nephropexy, and a partial oöphorectomy for dysmenorrhea.

For six years she had been under constant influence of self-administered sedatives because of sacral pain recently referred into the right posterior thigh unrelieved by tonsillectomy, hydrotherapy, heliotherapy, and psychotherapy including attempted hypnosis. She became lame nine months ago, falling several times.

Eight months ago there was flaccid paralysis of both lower legs. Vibratory sensation was impaired over the right tibia and ankle joint. Pain, touch, and temperature were denied completely over the sole of the right foot, and partially below the right knee. Laboratory findings were normal. The history of previous medication, an obvious toxic state, and complete reactions of degeneration below the right knee, warranted a provisional diagnosis of toxic neuritis at that time.

Five months ago an abortive right ankle clonus appeared. Four months ago the thigh muscles bilaterally showed increased tonus. Shooting pains in the lower lateral thighs, referred into the lumbar spine, became more severe, appeared oftener, and were associated with sudden intense contractures of the thighs on the hips. Occasional urinary and fecal incontinence developed. Three months ago right ankle clonus persisted. Continued spasticity in the thigh muscles appeared with paroxysmal spastic contractures, occurring every 10 to 15 minutes. The right knee jerk became increased. Sensory loss developed in the distribution of the twelfth dorsal, the lumbar, the first and second sacral spinal nerve segments. Another spinal puncture now revealed golden yellow fluid, strongly positive for globulin. A diagnosis was

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made of extramedullary spinal cord tumor. Laminectomy revealed the tumor extending from the eighth to the twelfth thoracic vertebrae. It was successfully removed.

Since operation there has been improved sensation and use of the lower extremities. The patient's behavior, however, has remained typically neurotic. After the provisional diagnosis of toxic neuritis was made, eight months' continuous observation was necessary to establish a correct diagnosis. It had been necessary also to make repeated neurological examinations in order to sift out of a galaxy of bizarre symptoms and signs the above changes dependent upon the organic lesion.

Case 2. A housewife, 38 years old, complained of nausea, emesis, headache, diplopia, diffuse muscular soreness and aching pain in the left shoulder. For a year there were intermittent attacks of numbness and partial loss of strength in the left hand and forearm. For two months there had been intermittent weakness. She had become unconscious twice.

She had always been nervous. Nausea was felt when she heard unpleasant noises. She worried about a possible developing arthritis, uterine cancer, her husband's health, and financial losses. Eight years before she had collapsed following her husband's nervous breakdown. She had had yearly attacks of influenza since 1918. A four year old son, hyperactive and mischievous, caused constant anxiety. A year before she was in an automobile accident which produced great shock. Four months before she had had an acute attack of tonsillitis with subsequent tonsillectomy and postoperative hemorrhage requiring sutures.

The only positive physical finding was a transient bilateral squint which she said had been present since childhood.

After six weeks there was twitching of the muscles in the upper left face and intermittent occipital headache. A week later there was numbness in the left face, and rapid loss of power in both lower legs. She then recalled a similar first attack which had occurred seven months ago. There was now a beginning neuroretinitis, and decreased sensation in the mandibular branch of the left fifth cranial nerve. She also recalled an attack of clonic contractures in the left upper arm with severe left cervical pain. The spinal fluid was under 56 mm. mercury pressure. Other laboratory findings were normal.

A neurosurgeon found no definite evidence of an organic lesion, but requested that she return again in six weeks. Craniotomy then revealed "a very deep glioma of the parietal lobe."

Thus, we see that an emotional fog had successfully obscured the three cardinal features of a brain tumor.

Case 3. A Russian Jew, aged 49 years, complained of diffuse headache for two months, worse at night and when coughing. He had been a professional boxer, and drank alcohol to excess. He was much depressed, cried, worried about financial losses, and slept poorly. There was pain in the lower anterior chest, and for three weeks clotted blood was observed in his sputum. He had been told four months ago that he had heart trouble.

His pupils reacted sluggishly, incompletely and irregularly. His blood pressure was 160 systolic and 100 diastolic. The cardiac apex was palpable in the fifth interspace 2 cm. to the left of the left midclavicular line in the recumbent posture. Finger to finger test showed past pointing. Roentgenograms disclosed a dense shadow occupying the greater portion of the left lung field, appearing nodular under the fluoroscope. The heart, aorta and trachea were displaced to the left. The appearance suggested a new-growth.

Patient returned home for a week, developed a hemiparesis, and was taken to a clinic where bronchoscopic examination revealed a lesion involving the left main bronchus. The growth bled easily. It was clinically considered malignant, although a biopsy showed only inflammatory tissue. An intracranial metastatic growth was also considered to be present, and he died a few weeks later.

Business reverses suggested a cause for complaints in a patient, who for several years had sought escape from unpleasant facts in alcoholic sprees. Roentgen-rays of the chest and bronchoscopic findings finally established an organic basis for his illness.

Case 4. A married woman, 31 years old, began to complain two years ago of agonizing rectal pain aggravated intensely by defecation. Nine months ago she had recovered from influenza, and roentgenograms of her chest had shown enlarged hilum glands to which an elevation of temperature was attributed. She was finally taken to a neuropsychiatrist, who learned that her husband had been without a position for six months. Their mortgaged home might be lost. A nine year old son, with cerebral spastic diplegia, required constant care which could not be hired. Her husband's parents had little sympathy for their predicament. She had given up her study of music to which she had been devoted. Her husband accepted his parents' opinion even concerning routine household matters. She was sent away for treatment of her nervous state. She was in a hopeless, puzzled, depressed state of mind, her mental anguish probably worse than her exquisite, constant rectal pain. Examination showed a tender rectal mucosa exuding pyoid material. Complete relief of pain followed excision of a perirectal abscess and hemorrhoids.

Explanations to the patient and interviews with her husband directed toward increasing his understanding of her situation and the necessity of institutionalizing their child have enabled the patient to adjust herself to her situation and return home.

On physical examination, a perirectal abscess was found to have caused the pain which for two years was believed to be of neurotic origin.

Summary

Neurotic behavior may mask organic disease so that it is unrecognized. In caring for the neurotic patient, it may be necessary sometimes to withhold judgment and examine the patient repeatedly in order to establish conclusively a correct diagnosis.

RELATION OF ERYTHEMA NODOSUM AND RHEUMATIC FEVER; A CRITICAL SURVEY *

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The etiology of erythema nodosum has been a source of considerable controversy which has not abated, despite the acquisition of what is considered to be fresh and decisive knowledge on certain aspects of the subject. The point of view expressed will often depend on the nature of the branch of medicine practiced and the country from which the report emanates. Broadly envisaged, there are four principal schools of thought: (1) those who regard erythema nodosum as a specific independent entity; in this group are ranged the dermatologists (Tachau [1]) and an occasional internist (Lendon's nodal fever [2]); (2) those who consider it to be chiefly, if not entirely, dependent on the factor of tuberculosis; in this category are to be found the pediatricians; (3) those who are of the belief that the eruption represents one of the rheumatic manifestations proper and, as a sub-class, those who are of the opinion that the skin lesions are of streptococcal origin; this group is composed preëminently of internists; (4) finally, there is an eclectic category of observers who consider erythema nodosum as attributable to a variety of causes, using as its chief argument the point that the rash has been encountered in the course of a host of maladies.

The principal purposes of this critical survey will be: (1) To discuss in some detail the alleged relation between erythema nodosum and rheumatic fever, a view which has numerous adherents today. While it cannot be denied that skin lesions of this type may be encountered under certain circumstances in the course of rheumatic fever, it appears that the data compiled in the past to substantiate this association are subject to much valid criticism. No attempt will be made to review the interesting streptococcal hypothesis, as the data which have come to light are too meager and inconclusive as yet. (2) To point out that the establishment of the diagnosis of erythema nodosum is by no means a simple procedure in all instances; and that the morphologic attributes of this eruption and of others simulating it are in want of further study and of critical analysis. Much of what has passed as erythema nodosum belongs, in reality, to another category of disease. It is apparent that in the pursuit of this problem the coöperation of the dermatologist with the other branches of medicine would be mutually profitable.

Historical Aspects

In the middle of the nineteenth century erythema nodosum was generally classed as "arthritic" or "rheumatic." In 1859 G. Sée [3] concluded, on

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the basis of clinical observation, that the joint pains encountered in this affection differed from those observed in rheumatic fever; that they represented a special type of arthralgia occurring before, during, or after the appearance of the eruption; that they were not characterized by redness of the overlying skin and swelling of, or serous effusion into, the affected joints; and, finally, that the articulations were capable of active and passive motion. It was also known at this time that the use of anti-rheumatic drugs was generally without avail. Trousseau [4] was of the belief that erythema nodosum was a specific disease, separating it from rheumatic fever since, as he stated, "I have never seen redness or swelling in the situation of the affected parts; nor have I ever found signs of cardiac lesion." Barlow,[5] on the basis of extensive observations in children, remarked that, "Erythema nodosum, it is well known, is associated with severe pains in the limbs and some fever and is sometimes followed, as rheumatism is, by considerable anemia. But I have never been able to assure myself of the production of an organic murmur in this disease, nor of any intercurrent arthritis, however slight; and it seems possible that the pains in the limbs may be accounted for, in great measure, by the effusions which, though limited in amount, often occur in spots which do not readily yield as on the front of the shins." Harrison [6] pointed out that erythema nodosum does not, as a rule, recur whereas this is a striking characteristic of rheumatic fever. Garrod noted that ". . . case after case presents itself in which the malady runs its course without implicating the heart, and this even in children who, as a class, show so great a liability to the cardiac accidents of rheumatism." West [7] criticized the laxity with which the term rheumatic fever had been used in the past and he stated: "This is especially true of erythema nodosum, which is still often called rheumatic because of the pains and fever; yet I have never seen erythema nodosum occur in the course of rheumatic fever, nor have I myself observed morbis cordis develop in the course of erythema nodosum, though I know such cases have been described."

Despite the doubts expressed by numerous able clinicians whose combined experience included observations in both children and adults, it is still currently accepted that erythema nodosum per se represents in part, at least, one of the rheumatic manifestations. Perhaps the most famous exponent of this view was Stephen Mackenzie [8a] who presented a paper (1886) based on a study of 108 cases of erythema nodosum. In 17 instances acute and subacute rheumatism were found associated. The criteria for the diagnosis of rheumatic fever rested on the occurrence of combinations of tonsillitis, fever, sour sweats, joint pains, and heart murmurs. However, close scrutiny of this report reveals that in many cases the only signs and symptoms, apart from the eruption itself, were joint pains and fever. Of the 17 instances cited textually, the thirteenth is of particular interest, as postmortem examination was performed; the patient, a female of 18 years, had suffered from erythema nodosum in the first, second, and third attacks of "acute rheumatism," and finally was observed in the sixth recrudescence of

" rheumatism," accompanied by the eruption for the fourth time, yet necropsy examination disclosed no abnormalities of the heart. It is, of course, realized that this study could not, at that time, have embraced search for myocardial Aschoff bodies or of interstitial valvulitis, both of which may rarely occur in the absence of gross evidence of endocarditis. Nevertheless, it seems improbable that the patient had experienced six attacks of rheumatic fever in the sense in which that disease is understood today. Mackenzie included 17 additional cases of doubtful nature and, on the basis of his statistics, concluded that erythema nodosum per se is a rheumatic manifestation, even in the absence of other signs and symptoms. In 1896 Mackenzie [8b] presented a comprehensive report based on the study of 125 more cases, which, together with his first group, totaled in all 233 patients. Of the combined series 43 or 19 per cent had suffered from what he called " undoubted articular rheumatism." An additional postmortem examination of a woman 47 years of age again revealed no abnormalities in the heart. These observations at necropsy tend to cast doubt, therefore, on the validity of the criteria used by Mackenzie for the diagnosis of active rheumatic disease. It seems curious that in reporting so large a series of cases, the factor of drug etiology as one of the possible causes of eruptions simulating erythema nodosum was not mentioned.

Clinical Data

In the course of the following presentation, a number of statistical compilations will be cited. The figures are, however, not to be regarded in an arbitrary manner, as individual experiences vary greatly; it will be more instructive to take heed of the general principles involved.

1. *Tonsillitis.* Erythema nodosum is accompanied by sore throat in a considerable proportion of cases, the latter being considered by Symes [9] as the most common prodromal complaint. The average incidence of antecedent angina appears to be about 20 per cent (Bücher,[10] 18 per cent; Hegler,[11] 20 per cent; Rolly,[12] 26 per cent). Hegler observed that the eruption succeeded sore throat after an interval of from three to seven days; others claim this period to be as long as 14 days or more (Symes), and it is possible that this symptom may be forgotten by the patient when the skin lesions make their initial appearance. Collis [13] recorded an instance in which the dermatosis occurred after each of five separate attacks of tonsillitis. I have encountered several examples where this sequence of events was observed on two or more occasions. On the other hand, sore throat may first become manifest during the course of erythema nodosum or even subsequent to it. Skin lesions may also appear in the wake of other varieties of oral infection, such as alveolar periostitis (Arborelius [14]).

The incidence of sore throat will depend, in great measure, on the type of material studied. In a dispensary service, where milder instances of the disease are seen, tonsillitis is a prodromal complaint in only a small proportion of patients, roughly in about 15 per cent, when average care is exercised

in taking a history. In patients with symptoms of sufficient severity to warrant hospitalization, the condition is more common, estimated at from 40 to 60 per cent.

Some observers believe that the occurrence of antecedent sore throat is evidence favoring the rheumatic etiology of the dermatosis. Such evidence per se does not, however, warrant this broad generalization, for it is known that tonsillitis may precede or accompany other affections having no particular relation to rheumatic fever. Moreover, the "rheumatic sore throat" appears to possess no pathognomonic clinical features by which it can be differentiated from ordinary angina. Gueissaz [15] advanced the attractive hypothesis that the antecedent tonsillitis of erythema nodosum may pave the way for the rheumatic agent, but this theory is based on the supposition that joint involvement is necessarily synonymous with rheumatic fever. According to Hegler, there seems to be a parallel relation between the occurrence of sore throat and subsequent joint pains in erythema nodosum, but this association is by no means absolute.

2. *Joint Involvement.* In many instances the diagnosis of rheumatic erythema nodosum has been postulated on the sole basis of articular pains, encountered commonly in the course of erythema nodosum (Hegler, 67 per cent; Mackenzie, 19 per cent). It is likely that articular pains are more frequent than is generally supposed, and that the figure arrived at will depend, to a great extent, on the type of material available for observation.

Patients seen in an ambulatory dispensary service only occasionally complain of articular disturbances. Frequently these are so mild that persistent interrogation is necessary to elicit this information. On the other hand, it may be difficult to distinguish these pains from the local discomfort produced by skin lesions, particularly when the latter are situated about the joints. Redness of skin overlying joint areas appears to be most commonly caused by cutaneous lesions, less frequently by peri-articular involvement, and rarely by intra-articular disease; it may be a clinical feat to determine with accuracy which of these factors is in operation. Fever may be minimal or absent throughout the short period of observation. Such patients are seen once or twice thereafter and then discharged as cured.

On the other hand, cases admitted to the wards of a hospital often present severe concomitant constitutional symptoms. Fever is generally found and may even attain a height of 105° F. in exceptional instances. Progressive anemia may be noted occasionally. Usually the patient complains of moderately intense joint pains and while it is difficult to demonstrate definite intra-articular involvement, it is my impression that peri-articular disease was an occasional cause. In most instances the pains are of the nature of arthralgias. In the average case the symptoms are limited to the ankles and knees, but at times the joints of the upper limbs may be affected either simultaneously or subsequently, even in the absence of overlying skin lesions.

In the older literature the arthralgias encountered in erythema nodosum were designated as "rheumatoid" or "pseudo-rheumatic" for the purpose

of differentiating them from true rheumatic polyarthritis (Sée, Trousseau and others). Of 45 cases of erythema nodosum seen in adults, Hegler [11] noted rheumatoid pains in 21 patients (46.7 per cent). Comby,[16] in a study of 172 children exhibiting these skin lesions, encountered 21 instances with joint pains (12.2 per cent), whereas Kuhn,[17] also reporting on the disease in childhood, observed articular discomfort in but 2 out of 22 patients (9.1 per cent). There are many observers, particularly pediatricians, who deny the occurrence of joint manifestations in erythema nodosum. Comparison of statistics indicates a higher incidence of "rheumatoid" pains in adults than in children. H. Koch [18] has recently offered another interpretation of this phenomenon, claiming that there is no articular pain or swelling in association with erythema nodosum, but that the symptoms are produced by periosteal involvement; this he was able to demonstrate microscopically in one case. However, a single instance of periostitis, possibly the result of contiguous spread of the inflammation, does not warrant generalization.

The association of "undoubted articular rheumatism" with erythema nodosum was recorded by Mackenzie [8b] in 43 out of 233 cases (19 per cent) and by Hegler in 20 per cent of 45 cases; these observers were concerned principally with adults. In children Comby [16] reported but two instances (1.2 per cent) in a series of 172 examples of the skin disorder. Comparison of statistics again reveals a higher incidence of joint involvement in the older age-group. The term "undoubted articular rheumatism," when defined precisely, referred to swelling of the articulations, a manifestation considered to indicate true rheumatic articular disease in every case. This view, therefore, requires qualification. There are, however, occasional descriptions of erythema nodosum accompanied by articular disturbances closely simulating these regarded as characteristic, but not necessarily pathognomonic, of rheumatic fever. Thus, cases have been recorded where there was migration of pains from one joint to another (Collis [12]); others in which the skin overlying the articulations was reddened, presumably from intra-articular disease (Patteson [19]); and still others in which the joints were exquisitely tender (Coburn [20]). However, these phenomena are relatively uncommon. Symes expressed the point succinctly when he stated that he had never observed in erythema nodosum the intense pain and fear of movement seen in acute articular rheumatism or gout, a statement with which my observations are in general accord. I have encountered occasional instances, particularly in adults, where there was an indefinite systematic progression of joint involvement simulating migratory rheumatic polyarthritis. At times pitting edema of the skin overlying articulations may be observed, especially in the vicinity of the ankles. These cases could usually be differentiated from true rheumatic polyarthritis by the absence of effusion into joints, of characteristic flitting from one part to another, of exquisite tenderness and fear of movement, by the retained ability for active and passive motion when care was exercised, and by the general therapeutic inefficacy of salicylate therapy. Broadly considered, these criteria apply in

the differential diagnosis from adult rheumatic fever, though it must be remembered that even in older persons, articular signs and symptoms may be just as atypical as in children. Nevertheless, it seems striking that erythema nodosum in adults rarely presents the features commonly encountered in typical rheumatic polyarthritis of the same age-group. In children, in whom articular symptoms are often atypical or lacking, other criteria must be invoked, particularly those concerned with evidence of cardiac involvement.

3. *Cardiac Disease.* (*a*) *Endocarditis:* Many authors (Hegler, Mackenzie, Kuhn, and Symes among others) have recorded the occurrence of transient systolic bruits at the apex or base of the heart in patients with erythema nodosum. Hegler, in particular, observed that occasionally the normal heart sounds may become impure, and that systolic murmurs may appear at the apex of the heart independently of the occurrence of articular pains. However, he recognized that genuine valvular defects, during or after the onset of erythema nodosum, "belonged to the rarities." Zuchholdt,[21] an adherent of the view that endocarditis is an associated finding, made the significant statement that termination in mitral stenosis was rare. The auscultatory evidence of cardiac bruits, in association with joint pains and, perhaps also, antecedent sore throat has influenced clinicians to classify such cases as rheumatic fever, when the tuberculin test is negative, but this view often lacks substantial proof. The deceptive nature of functional murmurs as revealed by postmortem examination need only be mentioned. Undoubtedly the older literature abounds with instances where accidental bruits were considered as of organic origin. Symes stated that he had never seen cases with persistent systolic murmurs; these transient bruits were, in his opinion, either haemic in type or due to temporary dilatation of the heart. In many instances varying grades of anemia may develop, probably accounting for some of the functional murmurs heard. The minimum evidence required to deduce a relationship between erythema nodosum and rheumatic fever is the demonstration of organically diseased heart, occurring either simultaneously or subsequently. This statement is offered advisedly, as it is realized that the *clinical* evidence for the recognition of cardiac disease may not be apparent at the time of examination. When, however, postmortem study is available, it seems fair to insist on this criterion, the validity of which appears to be gaining ground (Fahr [22] and others). No attempt will be made to describe the evidence of recent and old rheumatic involvement of the heart in its various forms, other than to state that there are ample criteria whereby the rheumatic nature of a case may be verified easily on microscopic examination (Gross). But the problem does not end with the demonstration of cardiac involvement, as will be shown in subsequent sections of this article.

From a clinical point of view, Gueissaz [15] reported 300 examples of erythema nodosum in children and adults, with not a single instance of concurrent endocarditis. Gosse,[23] in a series of 100 carefully studied cases in

all age groups, was unable to find any example of endocarditis, and subsequent observation failed to disclose cases with mitral stenosis or other valvular defect. Kundratitz,[24] Pollak,[25] Feer,[26] and Kuhn[17] among others were unable to discover a single instance of organically diseased valves in 81, 48, 45, and 22 children respectively with skin lesions of erythema nodosum. Of 86 cases of erythema nodosum observed in childhood, Ernberg[27] saw but one instance with valvular defect, but even in this isolated example he could not be certain of the relation. Comby, in 172 instances of the disorder in children, reported but two examples with coincident "acute articular rheumatism" and "mitral endocarditis," but he furnished no details relative to the precise nature of the valvular defect. Of 130 cases of erythema nodosum reported by Landau[28] in patients whose ages ranged from between 1 and 14 years, only once (0.8 per cent) was there an antecedent history of rheumatic infection; on the other hand, in 136 instances of rheumatic fever, Landau found a history of erythema nodosum in but four patients, an incidence which he regarded as no greater than that in other childhood disorders. I have observed many instances labeled as rheumatic erythema nodosum, owing to the occurrence of sore throat, joint pains, and a systolic bruit at the apex of the heart, but in no instance did the subsequent course disclose evidence of valvular defect, although some of the patients were followed for over five years. A distinction may be drawn between two types of cases: (1) where erythema nodosum occurs at the beginning of a febrile illness; (2) where erythema nodosum or lesions simulating it appear in a patient known to be afflicted with rheumatic heart disease. With regard to the first variety, the point should be stressed that such cases rarely, if ever, develop unequivocal evidence of rheumatic heart disease, when followed over a sufficient period of time. The recorded statistics on this phase of the subject, therefore, appear to be at variance with the view that rheumatic fever plays a major, or even a minor part, in the causation of this skin manifestation.

(*b*) Electrocardiographic observations have disclosed but few instances with significant abnormal changes. Master and Jaffe,[29] on the basis of daily electrocardiograms, concluded that: "Cases of erythema nodosum . . . revealed little evidence of myocardial damage and hence the relation to acute rheumatic fever is probably remote." Spink[30] observed that in 30 examples of erythema nodosum where serial studies of this type could be pursued, two cases showed evidence of prolongation of the P–R interval and one of myocardial disease. In evaluating data of this sort, it seems advisable to stress the points that (1) alterations in the electrocardiogram are not necessarily pathognomonic of rheumatic fever and are to be considered in terms of the entire clinical picture, as there are other diseases where similar changes may be encountered; (2) the criteria relative to prolongation of the P–R interval, particularly in border-line cases, vary with individual observers; this applies especially in the case of children; (3) the value of the fourth lead, as it concerns rheumatic fever, is still uncertain; this point is mentioned

as examples of erythema nodosum may be reported in the future with data bearing on this aspect of the subject; (4) finally, it remains to be noted that erythema nodosum or lesions resembling it may occur coincidently in the course of undoubted rheumatic fever; this point will be elaborated upon in subsequent sections.

(*c*) The simultaneous occurrence of pericarditis and erythema nodosum is extremely uncommon. In a survey of recent literature, Tachau [1] was unable to find a single instance of this combination. Coombs [31] has stated that this association is not necessarily diagnostic of rheumatic fever, for, according to this observer, it may occur in erythema nodosum complicated by tuberculous pericarditis and miliary tuberculosis. Pericarditis may also appear as one of the manifestations of bacteremia accompanied by erythema nodosum-like lesions.

4. *Chorea.* The association of chorea with erythema nodosum has been noted by a few observers (Garrod,[32] Mackenzie, Bass,[33] Claman [34]). Of 410 cases of chorea, Osler [35] found but one instance of this eruption or lesions resembling it. In a series of 100 cases of erythema nodosum, Gosse [23] encountered but a single instance of chorea; this he considered as indicating probable coincidence of diseases. The possibility of bromide or iodide erythema nodosum must be taken into account in cases of chorea where such medication may have been prescribed, as in a case observed by Bass.[36] Considering the evidence at hand, the association of erythema nodosum with true chorea minor may be regarded as rare.

5. *Subcutaneous Nodules.* The concomitant appearance of erythema nodosum and genuine rheumatic subcutaneous nodules is most uncommon. The association of the two manifestations has been reported by Weintraud,[37] Cheadle,[38] and, more recently, by Claman,[34] but it seems interesting to note that in at least the first two cases mentioned, the heart was not found to be involved. This appears curious when one considers the practically invariable occurrence of valvular disease with rheumatic subcutaneous nodules. I know of one example of this so-called combination of disorders, but in this case an erroneous interpretation of the phenomenon was offered; what was described as " rheumatic subcutaneous nodules " represented, in reality, the remains of lesions of erythema nodosum which had implicated the panniculus adiposus without marked involvement of the superficial skin. Cognizance must be taken of the point that when the efflorescences of this skin malady are abortive in type or in the process of involution, they may lie subcutaneously, so far as the palpating finger can tell. The possibility of calling them " rheumatic subcutaneous nodules " is not remote, especially when one is influenced by the opinion that erythema nodosum is a rheumatic manifestation. The greatest care must be exercised in describing as rheumatic nodules those lesions occurring subcutaneously at the former sites of an eruption of erythema nodosum, as the latter may leave nodular infiltrations, without redness of the overlying skin, when the panniculus adiposus is involved to

a major extent. This phenomenon appears to be more commonly encountered in the case of erythema nodosum of drug origin.

6. *Pleurisy.* With few exceptions (Wiborg [39] and others), implication of the pleurae has been uncommonly encountered in the course of erythema nodosum, except in the Scandinavian countries. Of 30 cases of this skin disorder, Wiborg reported eight instances manifesting evidence of pleural involvement; of his entire series, 26 were patients whose ages ranged from between eight and 15 years. This high incidence of pleurisy is nowhere duplicated or even approximated, except in reports emanating from Scandinavian countries where tuberculosis appears to be especially common. Moreover, these cases have been cited as proof of their tuberculous etiology rather than that of rheumatic fever. While symptoms of pleural involvement may occur in the course of rheumatic fever (pneumonia, pulmonary infarction, contiguous spread from pericarditis, hydrothorax, rheumatic pleurisy?), it seems doubtful that this isolated phenomenon can of itself establish the diagnosis of rheumatic disease. There are observers who have never encountered this combination of disorders. I have met with one such isolated instance exhibiting an unusually protracted course, but am unable to furnish information relative to the outcome. In any event, it appears that pleurisy is a relatively uncommon phenomenon in the course of erythema nodosum, except in cases recorded from the Scandinavian countries.

At this point it may be pertinent to mention the occurrence of a phenomenon that is foreign to the clinical picture of rheumatic fever, namely, the observation of hilar shadows in roentgen-ray pictures. The presence of hilar glands has been variously estimated at from 50 to 90 per cent of cases of erythema nodosum affecting children. I have seen several instances of this cutaneous malady in adults who likewise showed pronounced hilar shadows on roentgenologic examination, and it is likely that "hilitis" is more common in adults than has been suspected, this phenomenon being overlooked owing to its asymptomatic nature. It is not my purpose to discuss the significance of this manifestation, except to state that its etiology is uncertain as yet. Though the tuberculous nature of this phenomenon is accepted by most authorities, there are many lacunae in our knowledge of its nature.

7. *Salicylate Therapy.* On the basis of the alleged rheumatic etiology of erythema nodosum, salicylate therapy has been, and is still, used widely in this disorder. It appears to be clinically established that the pyrexia and joint pains of rheumatic fever usually yield in a striking manner to these drugs; however, similar results may be seen occasionally in other forms of arthritis. Gosse stated that salicylates have no influence on the essential course of erythema nodosum. Lendon abandoned the use of the drug as it had little effect on the pains and fever curve of erythema nodosum and the experience of Symes appeared to be similar in this regard. Whatever therapeutic results have been claimed for this form of therapy must be tempered by the knowledge that this skin disorder is generally of self-

limited course and of short duration. On the other hand, Hegler recorded an instance in which large doses of salicylates were powerless to prevent the appearance of the eruption.

8. *Activity in the Rheumatic Process.* In order to determine the relation of an eruption to rheumatic fever, it appears advisable to lay down the following practical postulates: (1) the disease process must be definitely one of rheumatic fever and the evidence must point towards activity in the disorder; to the latter part of this rule, there are some exceptions which will be discussed in another report; (2) the eruption must be related to the rheumatic process in such manner as to eliminate the possibility of coincidence of conditions. Relative to the first point, I have observed two instances of erythema nodosum appearing in patients with inactive rheumatic heart disease of many years' duration. Both were middle-aged women exhibiting signs and symptoms of mild congestive cardiac failure; subsequent observation failed to reveal clinical evidence of rheumatic activity. In one case the eruption had recurred at intervals during the antecedent two years; no attempt was made to prove a probable drug etiology, although it was known that she had been taking potassium iodide during this period. In the other case the dermatosis, morphologically resembling banal erythema nodosum in all particulars, was probably also caused by the intake of medication, as she had been using drugs to " relieve the nerves." It appears that the eruptions were in no wise related to the rheumatic process since in both instances, quite apart from their probable drug origin, they occurred in the absence of definite evidence of rheumatic activity. Had these patients come to postmortem examination, chronic valvular defects attributable to rheumatic disease would have been found in all probability, demonstrating the point that the observation of rheumatic heart disease post mortem in a patient previously afflicted with an eruption resembling erythema nodosum does not necessarily imply a relation between the two conditions.

In addition, I have encountered several instances of erythema nodosum occurring in association with rheumatoid arthritis, non-gonorrheal in type. These cases were characterized by the absence of evidence of rheumatic heart disease. Such examples do not necessarily warrant the belief that rheumatoid arthritis and rheumatic fever are conditions related to one another or caused by the same etiologic factor.

9. *Comparison with the Known Rheumatic Eruptions.* Although ordinary erythema nodosum may be characterized by the appearance of a few successive crops of lesions and by subsequent relapses of the condition in occasional cases, it appears to differ clinically from the known rheumatic erythemas of the popular, marginated or flat circinate varieties (Keil). The latter exhibit clinical attributes that remind the observer of the essential characteristics of the rheumatic process. They appear suddenly; their tenure of life is transient, lesions coming and going within a period of hours, occasionally one or more days; there is definite predilection for the trunk; they spread rapidly at their peripheries and have a marked tendency to form

configurations and bizarre shapes; there are usually many crops of lesions and, in occasional instances, they exemplify the chronicity of the rheumatic process by appearing at sporadic intervals over periods of months, and, rarely, even of years; there is generally associated undoubted evidence of heart disease, if not simultaneously, at least subsequently; and they are often accompanied by such rheumatic stigmata as transient subcutaneous nodules and chorea. The clinical course of an individual lesion is far more rapid and dynamic than in the case of erythema nodosum. On the other hand, the latter disorder, occurring at the inception of a febrile illness and being followed by undoubted evidence of cardiac involvement, is exceedingly uncommon.

10. *Pathologic Features.* The absence of characteristic Aschoff bodies in erythema nodosum cannot of itself be used as an argument against its rheumatic origin, as this seems to be likewise true of the microscopic anatomy of the known rheumatic erythemas, concerning which, however, more study is necessary. Some observers are drawing etiologic conclusions on the basis of similarities in histologic alterations to the lesions described by Klinge.[41] For example, Coburn [40] reported the case of a young woman who had erythema nodosum followed by polyarthritis. On the basis of the joint symptoms and the microscopic findings in sections of skin, he concluded that the eruption was of rheumatic origin. Histologic study disclosed vascular changes characterized by " swelling of endothelial cells which appeared frayed out into the lumen " and " escape of erythrocytes through the wall of the vessel, causing hemorrhage into the surrounding tissues. . . . Throughout the connective tissue and fat, there were scattered foci of infiltration by polymorphonuclear leukocytes. There were also areas of swelling of the fixed tissue cells and an edematous appearance of the tissue itself. In one or two of these areas, multinucleated cells were seen." While swelling of the collagen bundles of the skin as well as vascular changes accompanied by intense edema of the parieties may present gross similarities to the type of lesion described by Klinge, it seems fair to note that such pathologic alterations have not been demonstrated beyond peradventure to be necessarily pathognomonic of rheumatic fever. The histologic description recorded by Coburn corresponds with that observed in banal erythema nodosum (Symes), even to the presence of giant cells which apparently represent a reaction to foreign bodies (particularly fat products) formed in the panniculus adiposus. Similar pathologic alterations may be encountered in cases of erythema nodosum where there is no definite evidence of rheumatic fever. This is one instance where clinical study seems to yield data of greater importance than that furnished by the pathologic approach.

Considerations on the Morphology of Erythema Nodosum

The typical morphologic features of erythema nodosum need not be described, as the classical features are familiar to all. However, there are many atypical variants, the recognition of which is often difficult and the

status of which is generally uncertain. The ordinary evolution in the manner of a bruise (dermatitis contusiformis) is occasionally lacking or inconspicuous, the lesions presenting a delicate rosy hue or a faint purplish blush. Rarely, the eruption may be disposed unilaterally (diagnosed commonly as osteomyelitis, erysipelas, or septicemia) or a few efflorescences may appear on the contralateral limb either simultaneously or subsequently. While the lower extremities are the favored sites, it is not uncommon to find crops of lesions, usually of the small papular type, scattered on the upper extremities, notably about the elbows and wrists. In atypical situations, as on the face, lesions frequently reveal marked exudative qualities simulating the erythemato-vesicular type of erythema multiforme exudativum. In a considerable percentage of cases, eye lesions diagnosed as phlyctenular conjunctivitis or as episcleritis have been encountered; that these manifestations represent either rheumatic or tuberculous changes seems to be unproved as yet, though many investigators are in favor of the tuberculous etiology. Other observers have recorded the occurrence of oral mucous membrane lesions, an extremely rare manifestation with uncertain status. Lendon described splinter hemorrhages under the nails (Verco's sign) as part of the clinical picture of erythema nodosum. However, this phenomenon has not been encountered by other observers as well as myself and its status is also considered sub judice; painful subungual splinter hemorrhages are most commonly met with in subacute bacterial endocarditis, while, more rarely, massive extravasations of blood into the nail beds may be seen in " systemic " lupus erythematosus. The pseudo-fluctuant character of many lesions of erythema nodosum is probably caused by liquefaction of the neighboring subcutaneous fat when the inflammatory process affects the panniculus adiposus, but spontaneous resolution occurs without resultant necrosis or ulceration of the overlying skin. When an eruption is composed of elements that break down, there is reason to doubt the validity of the original diagnosis of erythema nodosum.

Galloway [42] stated that he had observed two types of lesions in this skin disorder; the papular and large nodular varieties. However, he made no attempt to differentiate them etiologically, nor did he cite illustrative cases. In a more recent publication, Collis [13] has proposed separation into the following two morphologic and etiologic categories; first, the large nodular florid type attributed to rheumatic fever or, more generally speaking, to streptococcal infection; second, the small nodular (papular?) form associated with tuberculosis. Relative to the rheumatic variety, the evidence presented, thus far, to adduce a relationship appears to be inconclusive. Although the classification advocated by Collis is not entirely acceptable on morphologic grounds, it has the merit of stimulating interest in clinical minutiae as a means of etiologic differentiation.

It is not my purpose to discuss fully the differential diagnosis from a strict dermatologic point of view, but rather to point out certain principles illustrating pitfalls in the classification of eruptions simulating erythema

nodosum. In making this attempt the account will necessarily have to be incomplete, as the principal design will be to draw on personal observations, completing them with the opinions of other investigators. It will be shown that much of what has been quoted in the literature as erythema nodosum belongs in reality to another category of disease.

(*a*) *Erythema Multiforme Exudativum.* This disorder, originally described by Hebra, presents a series of typical clinical phenomena, and in its ordinary form is easily differentiated from erythema nodosum. Like the latter disease, it has also been attributed to "rheumatism" but the evidence speaks clearly against this view (Tachau, Keil). The dermatosis may be associated with lesions on the lower extremities where, owing to the influence of location, they are apt to be somewhat nodular, show a cyanotic hue, and reveal tenderness on palpation (Veiel [43]). This variation has been attributed, in large measure, to the superimposition of an element of circulatory stasis and it is this type that is often described as erythema multiforme exudativum combined with erythema nodosum. There are, however, occasional border-line instances, notably when erythema nodosum takes on exudative qualities, where differential diagnosis is most delicate. Despite the latter occurrence, it would be unwise to regard the febrile forms of these disorders as identical, without further study of so-called transitional instances. In its classical form, erythema multiforme exudativum, a well-characterized disease, differs radically in the location, morphology, and clinical course of its skin and mucous membrane manifestations.

(*b*) *Erythema Multiforme of Rheumatic Origin.* Here we enter on a somewhat delicate subject. Many years ago Garrod [32] recognized the influence of the factor of location on the morphology of rheumatic dermatoses, when he described papular and marginated eruptions on the trunk in association with nodular painful lesions on the lower limbs. Josias [44] mentioned a similar observation. I have encountered an example of the phenomenon displayed by isolated lesions situated on the inferior extremities in a case of active rheumatic heart disease; to have labeled this eruption as erythema nodosum would have been stretching the point far beyond the criteria set down for the diagnosis of the latter disorder. Such dermatoses are always labeled erythema nodosum hesitatingly, though a review of clinical charts many years later may not lead to recognition of the uncertainties of the original diagnosis. In any event, the occurrence of small, somewhat painful lesions in the course of rheumatic fever does not necessarily mean that the eruption in question was that of erythema nodosum. The principle that skin lesions situated on the lower limbs may acquire attributes simulating erythema nodosum is also borne out by study of other dermatoses.

(*c*) *Chronic Bacteremia.* Isolated skin lesions of painful and nodular character may be encountered occasionally in the course of various forms of bacteremia in the acute as well as the more chronic types, but notably in the latter variety (subacute bacterial endocarditis, chronic meningococcemia,

gonococcemia, enterococcemia, etc). Because of their physical attributes, these eruptions are often classed as examples of atypical erythema nodosum; unlike the latter disorder, the lesions are generally discrete and few in number, are situated at other sites of predilection (especially the upper limbs), do not show the characteristic gamut of color changes, and undergo involution in a short time, usually measured in hours to one or two days. In their physical characteristics, they are strikingly analogous to the Osler Node, a term generally applied to the painful lesions observed on the finger tips, toes and other parts in subacute bacterial endocarditis. I have seen cases of chronic bacteremia diagnosed as rheumatic fever because of the presence of skin lesions, fever, polyarthralgias, functional or organic heart murmurs, and even prolongation of the P–R interval in electrocardiograms. Blood culture studies are usually of prime aid in establishing a correct opinion; sometimes the finding of the causative organism in sections of skin may provide the first clue. The difficulties confronting the clinician in the face of nodular painful eruptions accompanied by a clinical picture resembling rheumatic fever are therefore apparent. These skin lesions are not representative of true erythema nodosum and should not be labeled with this name; otherwise, the subject will become necessarily complicated by the introduction of miscellaneous dermatoses.

(*d*) *Tuberculides.* There is a more acute variety of erythema induratum revealing transitions to papulo-necrotic tuberculides and resembling erythema nodosum. Of this variant I have encountered three examples, characterized by the occurrence of cervical lymph node tuberculosis, typical papulo-necrotic lesions about the elbows, and painful, purplish red, nodular efflorescences on the lower limbs. The latter simulated ordinary erythema nodosum, the resemblance being further promoted by the failure to ulcerate and the assumption of an intense purple hue in the course of gradual involution. They differed, however, in their longer duration, in their association with typical lesions of papulo-necrotic tuberculides (some of which failed to show the characteristic central necrosis), and in the presence of chronic active tuberculosis of the lymph gland variety. It is possible that this type may be more properly labeled as papulo-necrotic tuberculide with atypical lesions on the lower extremities, the physical attributes of the latter being markedly modified by location.

I have also encountered several examples of non-ulcerating erythema induratum (Bazin type) in which the dermatoses were diagnosed as erythema nodosum owing to the painful nature of some of the lesions. It is possible that cases of this type may be given the title of chronic erythema nodosum. It is my belief, however, that erythema nodosum is chronic only in the sense that many relapses of the eruption may occur or, in the absence of recurrent cutaneous manifestations, that constitutional symptoms, such as fever, continue unabated over a relatively long time; the appearance of skin lesions for many weeks is not necessarily an indication of longevity

in the individual efflorescences, but rather is ascribable to the superimposition of fresh crops on fading lesions.

(*e*) *Syphilides.* It appears from the accounts of several observers, notably that of Hoffmann,[45] that there are instances of secondary syphilides resembling ordinary erythema nodosum. The precise status of this rare group is still unsettled; some of the cases seem to be instances of secondary syphilides with specific involvement of blood vessels of the lower limbs and elsewhere, resulting in skin lesions apparently indistinguishable from erythema nodosum; others may be examples of coincidental banal erythema nodosum; still others, of drug eruptions, particularly those caused by iodides or bromides; and, finally, some cases may represent instances of gummas that have resorbed completely without concomitant ulceration. The importance of this group of cases, as described by Hoffmann, lies in (1) the possible confusion with banal erythema nodosum; (2) the similarities in clinical picture to that of rheumatic fever, since in several of the recorded examples "rheumatic pains" occurred (syphilitic periostitis?) and in occasional instances the joints were said to be have been swollen and red. Since the publication of Hoffmann's comprehensive report of 11 instances of secondary syphilides resembling erythema nodosum, there have been but few additions to the casuistic literature and these, for the most part, doubtful in nature. How confused the subject has become is indicated by the citation (Spink [30]) of Stillians and Senear's [46] case as one of erythema nodosum syphiliticum; this case presentation provoked considerable debate relative to the status of the eruption and it seems interesting that the subsequent course revealed ulceration of the nodules in the manner of gummas. This instance cannot, therefore, be classified as an example of erythema nodosum. The entire subject of erythema nodosum syphiliticum is in need of clarification. No convincing proof has been recorded as yet that ordinary erythema nodosum may be a syphilitic manifestation; it is, however, granted that secondary and tertiary syphilitic skin lesions may occasionally present close clinical similarities to ordinary erythema nodosum.

(*f*) *Skin Lesions of Ulcerative Colitis.* The statement that erythema nodosum occurs in the course of chronic ulcerative colitis (Spink) has been based on the statistics furnished by Bargen [47] who in 693 cases of this disease, found 17 instances exhibiting skin lesions, particular mention having been made of erythema nodosum; no detailed case reports are, however, available so far as I was able to ascertain. From my own comparatively meager observations, it appears that this chronic disorder may be complicated occasionally by eruptions composed of nodular, painful, bluish red lesions, often called erythema nodosum at first sight; yet, further observation has revealed significant differences. In one striking instance, for example, the lesions which were situated on the lower limbs, and which at first seemed to be those of ordinary erythema nodosum, became filled with fluctuant bags of pus and then proceeded to break down. In another case efflorescences, similarly located, ulcerated rapidly. In still another example, there appeared

crops of painful, dull red papules over the upper and lower limbs, the dermatosis, however, lacking the ordinary physical attributes of erythema nodosum. The resemblance to erythema nodosum may be further promoted by the occurrence of joint symptoms which may occur in the course of chronic ulcerative colitis itself. Other observers have recorded analogous instances which may be conveniently divided into two arbitrary groups with transitions: (1) ulcerative lesions on the lower limbs, commonly termed pyoderma gangrenosum (Brunsting, Goeckerman, and O'Leary,[48] and Cohen [50] among others); larger areas of necrosis may also occur on other parts of the body, such as the trunk; (2) eruptions composed of efflorescences that early in the course may simulate erythema nodosum strikingly, but where subsequent observations reveal either spontaneous breaking down of lesions (Brooke [49]) or the formation of subcutaneous abscesses (Jones [51]). While the latter group may at first give rise to the clinical impression of ordinary erythema nodosum, it is apparent that the resemblances are superficial and occur only in the early course of the eruption. In studying the cutaneous manifestations of a disease like chronic ulcerative colitis which has experienced the gamut of medicinal therapy, it seems necessary to eliminate the possibility of drug etiology in every case of the disease.

(*g*) *Drug Eruptions.* This leads us into one of the most interesting and difficult phases of the problem, a more detailed consideration of which seems advisable in view of the high incidence of nodular painful eruptions of drug etiology.

It has been stated by Tachau [1] that nodular erythemas caused by drugs are distinguishable from ordinary erythema nodosum by virtue of the following features; their location may be atypical; the nodules are fewer in number and reveal tendency to necrosis; characteristic color changes do not appear in their further evolution; constitutional symptoms are lacking; and, finally, the eruption disappears when the suspected drug is stopped. However, these differential points do not hold for all cases, as there are many exceptions to the above stated rules. It is common knowledge, for example, that various medications may give rise to lesions that may simulate ordinary erythema nodosum in every morphologic detail. The problem becomes further complicated when drugs are administered for the alleviation of constitutional symptoms, such as fever and joint pains of various causes. However, in the average case absence of constitutional symptoms may be regarded as favoring drug etiology, but the latter should be verified by history of ingestion of the suspected medication, suitable laboratory tests (for example, urine examination for detection of bromides, etc.), and by other cutaneous evidence, such as the observation of a pustular eruption appearing simultaneously (iodides, bromides, etc.). In several instances of "halogen" erythema nodosum I have observed deep subcutaneous nodules which did not directly affect or discolor the overlying skin, substantiating Schidachi's [53] observations on iodide (nodose) eruptions; this phenomenon

is also encountered occasionally in idiopathic erythema nodosum, for reasons which have already been detailed.

Several difficulties may arise in determining the etiology of drug eruption simulating ordinary erythema nodosum. First, the history of ingestion of medication may be inadequate; second, laboratory procedures may be required to demonstrate the suspected drug; third, the patient may refuse to submit to therapeutic tests for purposes of reproducing the lesions *ex juvantibus;* fourth the absence of constitutional symptoms may not necessarily indicate a drug etiology as there are instances of banal erythema nodosum characterized by minimal or insignificant systemic reactions. It seems advisable to discuss these points which are commonly met with in dermatologic practice and which are sources of great difficulty. Appreciation of these difficulties is essential to the understanding of the problem as it relates to rheumatic fever. Dreschfeld [52] was among the first to suggest the possibility that lesions of erythema nodosum appearing in the course of rheumatic fever might be due to the ingestion of salicylates as he had personally observed this occurrence. Hegler recorded a case of rheumatic fever in which sodium salicylate produced a dermatosis simulating banal erythema nodosum; it differed, however, in the attendant pruritus and lack of color changes in its further evolution. Coburn described an instance of rheumatic erythema nodosum but the clinical attributes, such as itching and overlying vesicles, warrant suspicion of possible drug etiology; a dermatosis exhibiting these characteristics can hardly be classed as a typical example of erythema nodosum. In addition to salicylates, there are other drugs capable of producing skin lesions simulating banal erythema nodosum; among these may be mentioned quinine compounds, iodides, bromides, pyramidon, etc. It will be recalled, as a point of historical interest, that quinine and, in particular, potassium iodide were widely used in the treatment of rheumatic fever during the middle of the nineteenth century. The frequency with which iodides, for example, are capable of causing nodose painful eruptions is well known today, but apparently older observers were not aware of this point or did not take it sufficiently into account. On the other hand, there is a great tendency to suspect drug eruption merely because medication has been administered, leading inevitably to errors in diagnosis. Each case must, therefore, be individualized and, whenever feasible, an attempt should be made to prove the nature of the dermatosis by *controlled* therapeutic tests which, in final analysis, furnish the most decisive proof.

However, this procedure carries with it the possibilities of certain errors which should be recognized: (1) a given single dose of a drug may not reproduce the dermatosis *ex juvantibus;* in other words, eruptions are not always caused by marked hypersensitivity to a small quantity of medication, rather, a definite concentration of substance must be reached in the tissues before skin lesions occur. It is common knowledge, for example, that patients may take iodides or bromides for a long time before a dermatosis appears. I have also observed a case of " fixed " eruption caused by veronal,

where 10 grains of the drug reproduced the eruption, whereas 5 grains were without effect. The occasional statement found in the literature with respect to a latent period following the onset of a drug dermatosis, during which period the suspected medication is incapable of reproducing the skin lesions, needs substantiation in the light of the foregoing remarks. (2) It is necessary in trying the tests to eliminate the possibility of spontaneous relapses of the cutaneous manifestations, an especially common occurrence in erythema nodosum. It does not seem, however, from recent experimental work, that this factor has been sufficiently appreciated, and, unless one is exceedingly cautious, etiologic conclusions based on "therapeutic fallacies" may be drawn. Nonspecific effects also need to be recognized and evaluated.

It will be seen, therefore, from the foregoing comments, how many difficulties may present themselves in the diagnosis of an eruption as true erythema nodosum and how much care is necessary if one wishes to attack this problem in as scientific a manner as the subject permits.

Summary and Conclusions

The hypothesis that erythema nodosum represents one of the rheumatic series had its roots in the original communications by S. Mackenzie who was instrumental in popularizing it. This was accomplished during an era when the term rheumatic disease did not enjoy the precise meaning which it now possesses; the criteria employed by Mackenzie were, therefore, vague and much too elastic, a circumstance recognized by many of his contemporaries whose dissenting opinions were cited. Mackenzie's views are, however, still widespread among practitioners and, indeed, his statistical evidence is still quoted as corroborative of the hypothesis. When the diagnosis of rheumatic erythema nodosum is postulated, there is automatically conveyed to the mind of the observer the potentialities of subsequent serious cardiac disease, and it is for this reason that the subject assumes an importance far beyond the theoretical implications.

A number of recent investigators, recognizing that many cases reveal no evidence of rheumatic fever at any time, have adopted the eclectic point of view that a certain variable percentage of erythema nodosum is of rheumatic origin. Too often such beliefs are based on impression and no serious effort made to ascertain the fate of such patients. Complicating the problem has been the attempt of some observers to separate the disease as seen in children from that in adults, a point of view that does not seem to be corroborated by study of the disorder in all age-groups. When one analyzes the characteristics of the genuine rheumatic dermatoses (papular, marginated, and flat circinate erythemas of rheumatic fever), there appears reason to doubt that erythema nodosum belongs in the same category. As argument by analogy alone may prove treacherous, it was decided to study the entire subject in a critical manner.

At the outset, it must be emphasized that a condition as common as is rheumatic heart disease may be associated sometimes with erythema no-

dosum appearing as a coincidental and unrelated affection. It is probable that if observers were to look back upon their clinical experience, they would recall an occasional case of this type, where the occurrence of skin lesions had no appreciable effect on the heart disorder clinically, where the eruption resolved in a short time and the patient recovered within a correspondingly brief period without any mishap. In the text there were noted, also, two examples of coincidental erythema nodosum, probably of drug origin, appearing in patients afflicted with chronic inactive rheumatic heart disease, accompanied by mild congestive failure apparently of mechanical nature. What, on the other hand, is to be expected in persons who have never suffered from any of the various rheumatic stigmata, and who present, for the first time, the cutaneous manifestations of erythema nodosum at the inception of a febrile illness, accompanied by joint symptoms and other phenomena? Do these patients develop undoubted evidence of rheumatic heart disease?

The relation of such instances to rheumatic fever was analyzed in terms of the criteria set down for the diagnosis of the latter disease (sore throat, joint involvement, cardiac disease, chorea, subcutaneous nodules, pleurisy, salicylate therapy, active vs. inactive rheumatic disease, comparison with known rheumatic erythemas, and the pathologic features). The data recorded seemed to indicate that this alleged relationship rested on tenuous grounds; in many instances it was apparently not realized that the two disorders may present similar, but not necessarily identical or superimposable features; resemblances in clinical picture do not connote absolutely alliance between such conditions. It was further noted that many eruptions, frequently quoted in the literature as true erythema nodosum, were in all probability manifestations of another category of disease. This point was illustrated by brief citation of disorders confounded with erythema nodosum as seen within my own observations (erythema multiforme exudativum, erythema multiforme of rheumatic fever in its papular and marginated forms, skin lesions encountered in acute and especially in chronic forms of bacteremia, tuberculides of the papulo-necrotic or erythema induratum types, syphilides, cutaneous manifestations of chronic ulcerative colitis, and, most important of all, the nodular, painful eruptions of drug origin). Chief emphasis was placed on the principles illustrating pitfalls in diagnosis, rather than on a close dermatologic consideration of morphologic minutiae. It becomes apparent, in studying a problem of this sort, that the internist cannot rely solely upon his own knowledge of cutaneous manifestations, that reports in the literature must be evaluated with a critical eye, and that studies based on perusal of charts, while valuable and instructive, take second place to personal observation. Too often valuable details relative to eruptions are not recorded or a diagnosis of erythema nodosum may be made diffidently in the hope of subsequent confirmation which may not be forthcoming, but which is not apparent to the person reviewing the chart at a later date.

The relation of erythema nodosum to rheumatic fever is, therefore, a problem which should be investigated anew. Cases of this type must be studied over long periods of time in order to eliminate with certainty the possibility of clinically unrecognizable rheumatic heart disease. Every method of approach must be utilized, but the limitations of the various procedures must also be recognized. In patients with inactive rheumatic heart disease, erythema nodosum or lesions resembling it, may occur (*a*) coincidentally; (*b*) as a drug eruption; (*c*) as evidence of rheumatic activity; (*d*) under the guise of an erroneous diagnosis. In persons showing undoubted evidence of active rheumatic heart disease (rheumatic fever), the skin lesions may appear: (*a*) fortuitously; (*b*) as a drug eruption; (*c*) as a genuine manifestation of rheumatic origin; (*d*) as part of the nodose lesions seen in rheumatic erythemas; (*e*) as a wrong diagnosis. With regard to true erythema nodosum, it would seem advisable to study the disorder under two heads: (1) in its ordinary primary form, where the lesions appear at the inception of disease without previous evidence of rheumatic fever; (2) where the eruption occurs in a patient who is already known to be afflicted with rheumatic heart disease or has had stigmata of rheumatic fever. My own observations do not appear to substantiate the hypothesis that erythema nodosum is of rheumatic origin, even when preceded by sore throat and followed by joint manifestations. It will not do to label cases of erythema nodosum as tuberculous when the tuberculin test is positive and rheumatic when the reaction is negative.

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THE RELATION OF FUNGUS INFECTION OF GRAIN CROPS TO VASOMOTOR DISTURBANCES IN MAN *

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THE relationship of diseases of plants to human health has not received the detailed consideration which it deserves. Although botanists and agriculturists have made intensive studies of plant pathology, there has been no systematic effort to correlate plant disease with human pathology. On perusing the literature with a historical perspective it is interesting to note that the ancients ascribed disease conditions to contaminated cereal crops. Thus Galen refers to the " morbus cerealis," a disease due to eating spoiled cereal. There are also on record epidemics from eating bread made of rye infected with the fungus, *Claviceps purpurea.*[1]

Robertson and Ashby [2] have reported on the symptoms of ergotism found among the Jewish people of Manchester as the result of eating rye bread. The symptoms complained of were coldness in the extremities, numbness and lack of sensation in the fingers, formication, headache, gastric disturbances, shooting pains, twitchings in the limbs, and staggering gait. None of the symptoms were observed among those of the Jewish population who ate white bread. The rye grain examined at Manchester showed an incidence of 1 per cent infected with fungus.

Although the occurrence of epidemics of ergotism is a well known medical fact the widespread infestation of our cereal crops with *Claviceps purpurea, Ustilago zeae, Fusarium moniliforme* and other grain fungi has been rather overlooked or neglected as a fact of medical importance. *Claviceps purpurea,* the ergot fungus, occurs commonly on rye (Secale), and many other species of grass such as wheat grass, wild ryes, Kentucky blue grass, Canada blue grass, red-top, timothy grass, and occasionally wheat. The mycelium of the ergot fungus attacks the ovary of the plant while it is in bloom. The fungus consumes the ovary and replaces it with the ergot which consists of a dense mass of fungoid interwoven mycelium, a sclerotium (figure 1). Cattle fed ergotised grain or grass become emaciated and rough-haired. There is a disturbance in the circulation through the extremities, and gangrene of parts of the tail, ears, and hoofs may occur, as well as abortion.

After having published my preliminary report [3] on the etiologic relationship of these grain infestations to vasomotor disturbances such as erythromelalgia, Raynaud's disease, Buerger's disease, Schultz's acro-paresthesia, acrodynia, and hypertension it was called to my attention that J. Kaunitz [4] in 1930 had contributed a report on the pathologic similarity of thromboangiitis obliterans and endemic ergotism. His is the first report that I have

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read which attempts to establish the theory that ergotism of a chronic endemic type is responsible for Buerger's disease and related vasomotor disturbances. He notes that the ergot fungus attacks most of the grains and grasses and is present in most portions of the globe. It has been reported in every continent including Australia and New Zealand. Considering the amount of ergot-infected rye bread consumed, Kaunitz is surprised that cases of endemic ergotism are so rarely reported. He further states that it may well be that such conditions as thromboangiitis obliterans, Raynaud's

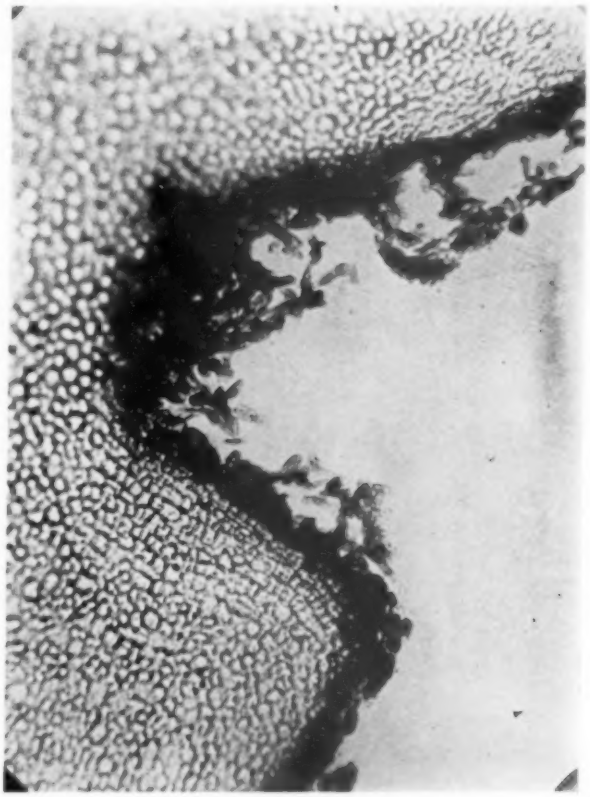

FIG. 1. Sclerotium of ergot fungus.

disease, as well as other vasomotor and trophic disturbances have been overlooked as possible sequelae to ergot poisoning. This may be because of the mildness of the original intoxication and the insidious onset of the vascular changes. Kaunitz further notes that both thromboangiitis obliterans and gangrenous ergotism have a preference for the male sex.

Another aspect of ergotism has been reported by Mellanby [5] who has demonstrated a very important fact with regard to diet and ergot toxin. On the basis of experimental studies he concluded that food rich in vitamin

A prevents the neurotoxic effects of ergot toxin; while a deficiency in vitamin A increases the degenerative effect of this poison. Furthermore, the addition of cereals and cereal embryo aggravated the degenerative changes induced by the ergot poison. Mellanby demonstrated experimentally that ergot could be consumed with impunity as long as the diet was rich in vitamin A and carotene. This fact is of decided clinical and therapeutic significance.

In the course of the present work I have examined samples of commer-

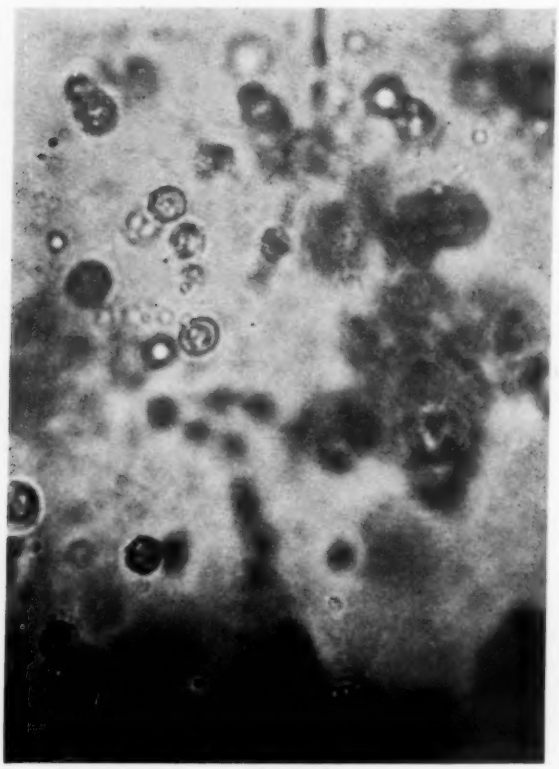

FIG. 2. Conidiospores of ergot parasite in commercial rye flour.

cial rye flour and pumpernickel bread (whole rye much used by our immigrant population, particularly Slavs) and have been able to demonstrate the conidiospores of the ergot parasite (figure 2). I have also examined corn meal bought in the retail market and have found the spores of *Ustilago zeae-mays* (figure 3). Corn is very frequently diseased (figure 4). Among the most common types of corn infestation are the smut fungi, *Ustilago zeae* (Koehler [6]). The outstanding characteristic of all the grain smuts is that they nearly always destroy the head or grain of the wheat, rye, barley, corn or oats affected. There are more than 600 species of these

grain parasites recognized, of which 205 are found in the United States. It is estimated by F. L. Stevens and J. B. Hall [7] that 100,000,000 bushels of grain are affected annually by the development of smut on corn, wheat, oats, rye, and barley. The common corn smut develops on any part of the corn plant but is much more conspicuous on the ears and tassels.

Intoxication occurring in children with all the symptoms of acrodynia has been reported by E. Mayerhofer.[8] In the spring of 1929 he observed two children from the region of Zagreb who presented all the manifestations

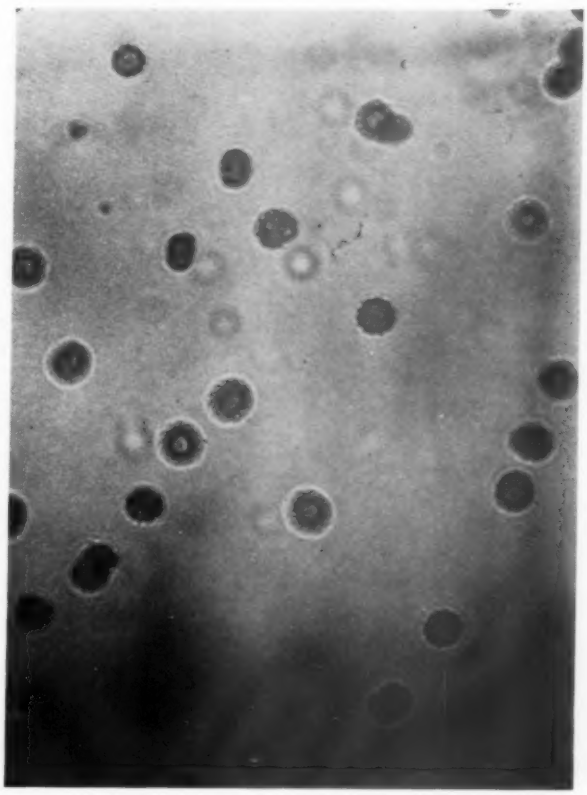

FIG. 3. Spores of *Ustilago zeae-mays* from cornmeal.

of ergotism or acrodynia and who had been fed on contaminated corn. A large content of *Ustilago zeae* spores was found in the corn flour. The intoxication had the pharmacologic and toxic characteristics of ergotism. Mayerhofer has expressed himself as seeing a causal relation between corn smut and acrodynia.

I have isolated ustilago spores from commercial corn meal and cultured them on sterilized corn meal media. After a heavy growth was obtained it was extracted with acid alcohol. The resulting product when injected into

an adult rooster caused a blackening of part of the comb, thus demonstrating the ergot effect and the vascular toxicity of the ustilago fungus. Sollmann [9] in his pharmacology notes that corn smut, or *Ustilago zeae,* has a mild ergot action and is frequently used to induce abortion among Southern negroes. A. Marie [10] made extracts of diseased corn and found that it had the properties of ergot.

The chemistry of ergot has been the subject of numerous thorough investigations. Various substances such as amines and alkaloids have been extracted. Dale [11] found that the action of ergot was due to the presence of

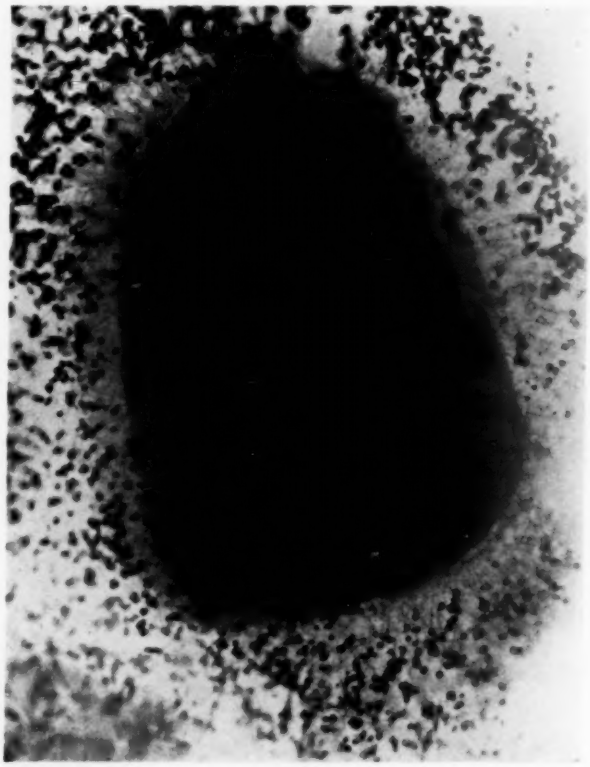

FIG. 4. Incubated corn kernel with ustilago fungi growing.

ergotoxine, tyramine, and ergamine. More recently Stoll [12] has isolated a crystalline alkaloid, ergotamine tartrate ($C_{35}H_{55}N_5O_5$), which is a chemically pure alkaloid and which has marked potency. It is a pharmacologic antagonist to adrenalin and inhibits the sympathetic nerve endings. It lowers the basal metabolism, causes a diminution in heat production and has a marked action on the uterine musculature. In a dilution of 1–2,000,000, it acts on the guinea-pig uterus and is thought to be the specific alkaloid of ergot. Human beings have been found to be more sensitive to its effects than animals.

I studied the effect of ergotamine tartrate on the white rat. A group of six young white rats were used for the ergotamine experiments and four were held as controls. A solution of two and one-half mg. of ergotamine tartrate was injected subcutaneously twice weekly for two months. The drug was also administered daily in the drinking water in the proportion of 0.001 gm. to 8 ounces of water. Early in the experiment there was noted a pronounced cyanosis of the tip of the tail in all of the six experimental rats. A dry gangrene of the tail developed in two rats after the first month. The experimental animals seemed quieter than the controls. One, however,

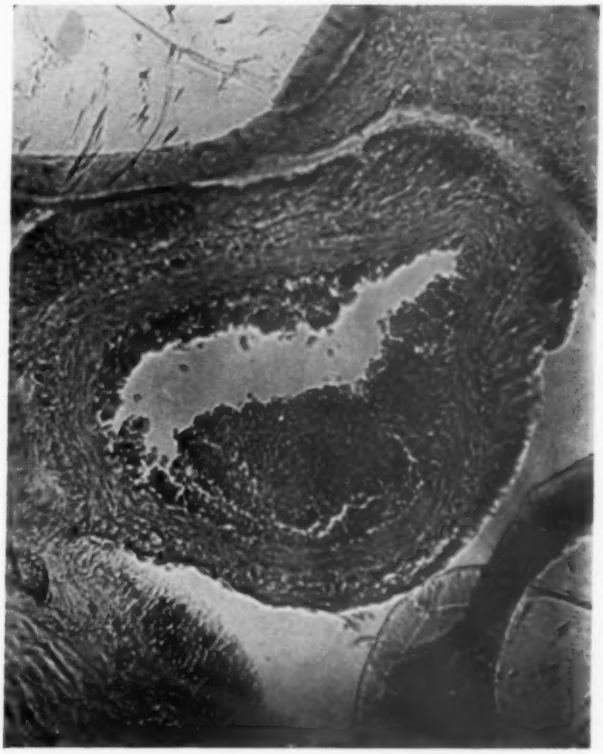

FIG. 5. Normal artery of rat's tail.

developed symptoms of excitation, ran about the cage, made unusual noises, and acted in a strange manner. After two months all of the animals were chloroformed and autopsied. No noteworthy abnormalities were found on the gross examination. On histologic study the tail arteries of the experimental rats were found to be very markedly constricted so that almost no lumen was apparent (figures 5 and 6). No inflammatory changes were observed.

The various theories proposed at present for the explanation of acrodynia do not seem to be satisfying or conclusive. Feer [13] has suggested that

the condition is a neurosis of the vegetative nervous system. This is considered plausible by many. Others, on the contrary, ascribe it to some unknown virus infection or even to a deficiency of vitamins. The pathologic findings in the few cases studied have been rather puzzling and unsatisfactory. Most of the attention has been centered on the state of the nervous system with very dubious results.

In view of the conflicting theories on the etiology of acrodynia, the theory that it is due to grain fungus intoxication is brought up for consideration on the basis of the above clinical and experimental data.

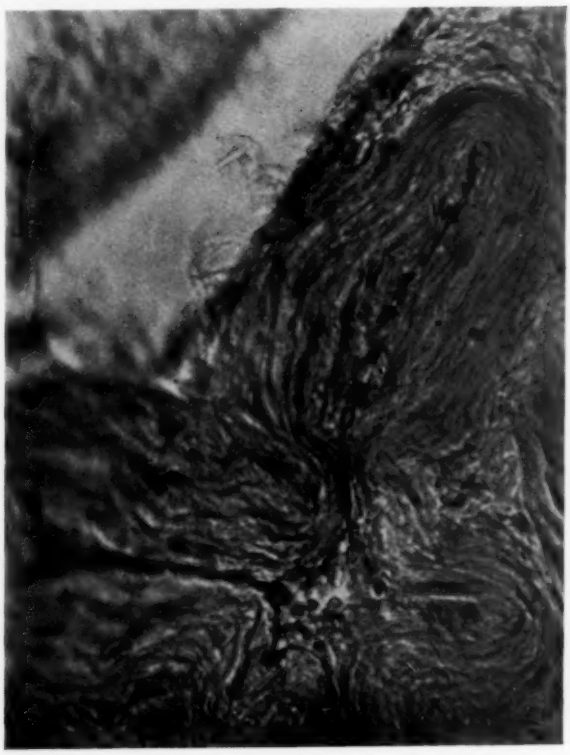

FIG. 6. Constriction of artery after ergotamine.

CONCLUSIONS

1. Our common cereals are frequently subject to fungus infection, particularly ustilago (smut) and *Claviceps purpurea* (ergot).

2. It is suggested that the ingestion of such food over a period of years may produce a chronic intoxication by the contained ergot alkaloids and amines which may be the cause of certain vasomotor disturbances such as acrodynia, Buerger's disease, erythromelalgia, Raynaud's disease, and acroparesthesia.

3. It seems advisable that serious attention be given to the problem of reducing these fungus infections of our common cereals by modern chemical treatment of infected seed and by improved milling methods.

4. Plant pathology is of considerable significance in relation to human health and should be systematically studied from this point of view.

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CASE REPORTS

BRADYCARDIA IN APPENDICITIS; REPORT OF A CASE*

By Mitchell Bernstein, M.D., F.A.C.P., and Ralph Goldsmith, M.D., F.A.C.S., *Philadelphia, Pennsylvania*

The occurrence of bradycardia in a patient manifesting acute abdominal symptoms which proved to be due to a gangrenous appendix prompted us to investigate this subject. It is interesting to note that in *The Journal of the American Medical Association* of December 1906, Maurice Kahn [1] directed attention to the presence of bradycardia in appendicitis. He stated that " in the last six cases of gangrenous appendicitis in which this symptom was evinced, the diagnosis of the gangrenous state was made before operation, based on the bradycardia alone. So it would appear from this that given a case presenting other unmistakable signs of appendicitis with a subnormal pulse, the tentative diagnosis of gangrene, with some reason, may be maintained."

Since the appearance of Kahn's original article several French and German authors have added other cases of similar nature to the literature. Von Bokay [2] in 1908 cited 10 cases of bradycardia in appendicitis in children. Although Kahn believed that the bradycardia in appendicitis was due to the absorption of ptomaines which acted on the cardiac centers or ganglia, Bokay believed the mechanism to be due to vagal stimulation. Broca [3] reported an instance of cardiac arrhythmia occurring in non-gangrenous appendicitis which was corrected when the appendix was removed and even before the patient had recovered from the anesthesia. Other cases in his experience of appendicitis and bradycardia are cited in which gangrene did not occur but abscess and adhesions were present. He emphasized the importance of observing the pulse and temperature relation in making a prognosis and determining the time for operation.

Vaquez [4] suggested the use of atropine to differentiate reflex bradycardia from that associated with a myocardial lesion of infectious origin. He reported a case in which a nervous patient in the course of an attack of appendicitis had considerable and persistent slowing of the pulse (40 per minute) with slight syncopal attacks. Atropine doubled the pulse rate and both the bradycardia and the syncope disappeared. Apparently, on the basis of this experience Vaquez and Laidlow [5] state that " it has been asserted that the bradycardia is a sign of danger; but this is an error. In one of our patients the bradycardia disappeared after the injection of atropine." These authors point out that bradycardia occurs in many different diseases, notably abdominal diseases and especially in appendicitis.

Loeper [6] reported a fatal case of appendicitis with bradycardia, that of a man, aged 38, with sudden onset of vomiting following right lower quadrant pain and fever. Improvement followed upon the application of an ice cap.

* Received for publication October 5, 1936.

From the Medical Service of Dr. Mitchell Bernstein and the Surgical Service of Dr. Ralph Goldsmith, Jewish Hospital.

On the third day, abdominal distention occurred, with pinched facies. The pulse which was 110 per minute lowered suddenly to 50 per minute despite the persistence of fever. Laparotomy revealed a gangrenous appendix and a collection of pus. Although drainage was instituted, a subphrenic abscess and right pleurisy followed and death occurred on the eleventh day after operation.

Bénard [7] studied the bradycardia in appendicitis by phlebogram tracings.

Decourt and Bascourret [8] observed that the concept of bradycardia of gastrointestinal origin seems much less well established than the usually accepted belief that certain gastrointestinal conditions may reflexly produce palpitation, precordial pain, tachycardia and extrasystoles.

The Mechanism of the Reflex Bradycardia

The mechanism of reflex bradycardia is explained by Howell [9] as follows: "The inhibitory fibers of the heart may be stimulated reflexly by action upon various sensory nerves or surfaces. One of the first experimental proofs of this fact was furnished by Goltz's [10] often quoted 'Klopfversuch.' In this experiment, made upon frogs, the observer obtained standstill of the heart by light, rapid taps on the abdomen and the effect upon the heart failed to appear when the vagi were cut. In the mammals every laboratory worker has had numerous opportunities to observe that stimulation of the central stumps of sensory nerves may cause a reflex slowing of the heart beat. The effect is usually very marked when the central stump of one vagus is stimulated, the other vagus being intact. The vagus carries afferent fibers from the thoracic and abdominal viscera, and most observers state that the heart may be reflexly inhibited most readily by stimulation of the surfaces of the abdominal viscera, by a blow upon the viscera, for example, or by sudden distention of the stomach. In man similar results are noticed very frequently. Acute dyspepsia, inflammation of the peritoneum, painful stimulation of sensory surfaces, the testes, for instance, or the middle ear, may cause a marked slowing of the heart,—a condition designated as bradycardia. What takes place in all such cases is that the efferent impulses carried into the central nervous system reflexly stimulate the nerve cells in the medulla which give origin to the inhibitory fibers of the heart."

The perennial question of the differential diagnosis between thoracic disease with abdominal symptoms and vice versa still remains an important problem in medicine. For instance, a case in point is acute coronary occlusion with its referred abdominal symptoms which often simulate gall-bladder disease. In our patient, the first symptoms suggested an acute surgical abdominal condition, but with the temporary subsidence of the abdominal symptoms, and the persistence of the bradycardia, it appeared that we were dealing with some cardiac derangement. However, the true nature of the process soon became apparent with the localization of the pain and the tenderness.

Case Report

F. M., an unmarried man, aged 30, was admitted to the accident ward of the Jewish Hospital on December 22, 1935 at 4 a.m., complaining of severe abdominal pain which had come on rather suddenly and had persisted for over two hours. The pain which was quite diffuse was of a dull aching character. Flatulence and belching were present but there was no nausea or vomiting. On admission, the patient's

temperature was 95° F., and the respirations were 16 per minute. A striking feature on examination was the cardiac rate which was recorded at 44 per minute. The cardiac examination otherwise was negative. The systolic blood pressure was 120 mm. of Hg and the diastolic pressure was 80 mm. Physical examination other than the foregoing was essentially negative.

The patient stated that he had had "encephalitis" for two weeks in 1922, from which he had apparently recovered. His tonsils had been removed in that year. He could not recollect any history of chorea, rheumatic fever or cardiac disease.

Following the routine physical examination, a fluoroscopic examination of the abdomen was made and was reported as negative.

At 11:30 a.m., seven and a half hours following admission to the accident ward the patient appeared quite comfortable and was free of pain. Curiously enough the bradycardia persisted; the heart rate averaged 42 beats per minute. Electrocardiographic study (figure 1) made at that time showed a sinus bradycardia of normal rhythm and a cardiac rate varying from 42 to 53 per minute.

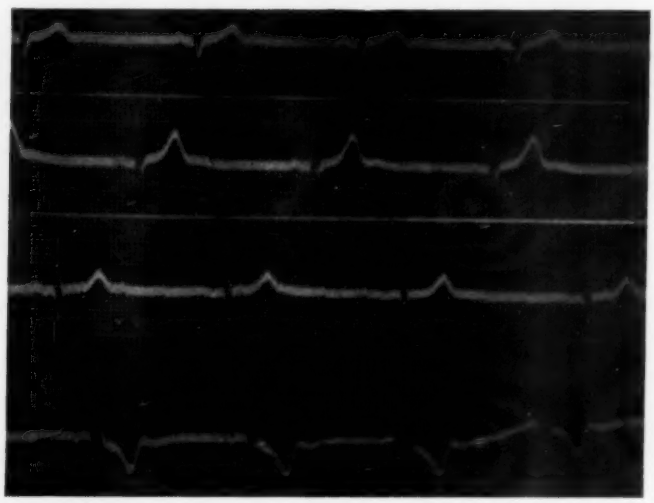

FIG. 1. Sinus bradycardia with ventricular rate varying from 42 to 53 per minute.

In view of the bradycardia associated with the acute abdominal symptoms, the patient was advised to remain in the hospital and he was admitted to the medical service of Dr. Mitchell Bernstein.

A blood count showed 10,850 leukocytes and 61 per cent polymorphonuclear cells, 36 per cent lymphocytes, two transitional cells and one eosinophile. Examination of the urine was normal.

On the afternoon of December 23, the day following admission, the patient again complained of pain, now localized to the right lower abdominal quadrant. Examination disclosed tenderness and muscular rigidity over this region, and the diagnosis of appendicitis was made. At 3 p.m. the cardiac rate rose to 70 per minute while the temperature was 102.6° F. A second electrocardiographic study (figure 2) showed a normal sinus rhythm with a cardiac rate of 68 per minute. The blood study showed 90 per cent hemoglobin, 4,650,000 red blood cells and 13,000 leukocytes per cu. mm. with 85 per cent polymorphonuclear cells and 15 per cent lymphocytes.

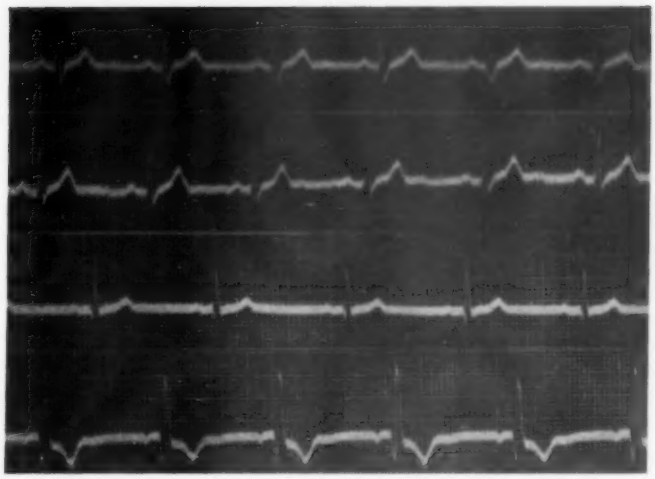

FIG. 2. Normal sinus rhythm with ventricular rate of 68 per minute.

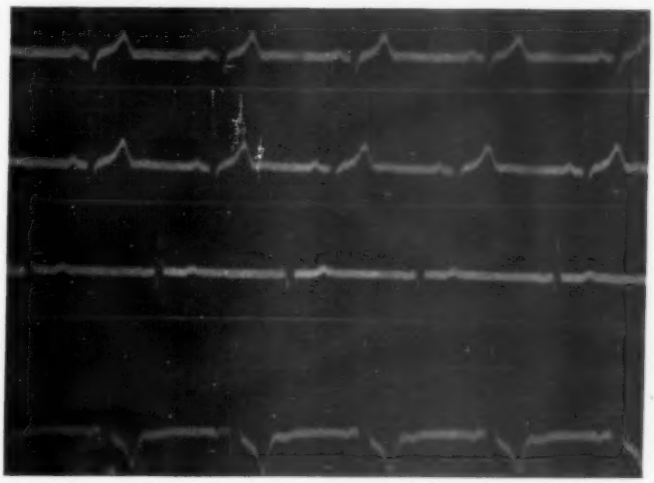

FIG. 3. December 24, 1935. Following operation. Sinus bradycardia with ventricular rate of 56 per minute.

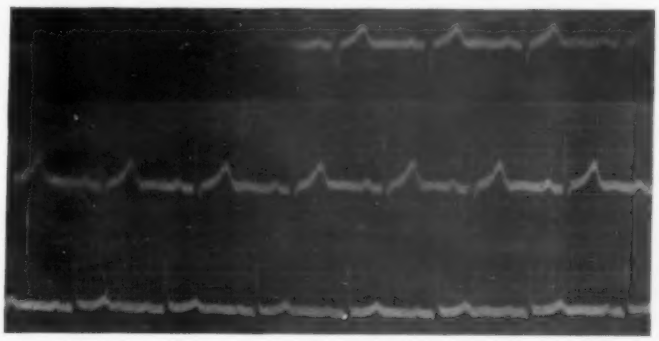

FIG. 4. December 30, 1935. Seven days after operation. Normal tracing with ventricular rate 77 per minute.

In the early evening the patient's abdominal symptoms became more severe. Dr. Ralph Goldsmith, concurring in the diagnosis of appendicitis, operated upon the patient immediately, under ether anesthesia, and removed an acute gangrenous appendix which was embedded in an omental pocket.

On December 24, the day following operation, electrocardiographic study (figure 3) curiously enough showed a cardiac rate of 56 per minute with a normal sinus rhythm. The patient's convalescence was uneventful.

Another electrocardiographic study (figure 4) on December 30, 1935, seven days after operation, showed a normal tracing with a cardiac rate of 77 per minute. Subsequent follow-up examinations of the patient on March 8, 1936 and July 2, 1936 showed the patient to be well. His heart rate was 72 per minute and following slight exertion it rose to 100 to 110 per minute.

Discussion

As has been stated, Kahn in his original article on bradycardia and appendicitis, believed the bradycardia to be due to the absorption of ptomaines which acted on the cardiac centers or ganglia. However, Howell's explanation of bradycardia in abdominal diseases as being due to reflex vagal stimulation, is the generally accepted viewpoint. While an understanding of this reflex mechanism is of importance, yet from a practical standpoint the interest in Kahn's paper centers in the clinical recognition of the associated bradycardia in appendicitis, in so far as it may mean the ultimate saving of human life.

That the diagnosis of gangrenous appendicitis is often difficult, especially in cases where the symptoms are latent or deceptive, is a fact well known to the experienced physician. Since the treatment of appendicitis is purely surgical, and since the treacherousness of the disease increases as the lesion progresses, any new sign or symptom useful in establishing a correct diagnosis should be carefully considered.

In our case, herein reported, the gangrenous appendicitis might have been overlooked with a probably serious result. In fact, Loeper's case of somewhat similar nature proved fatal. Although other writers such as Broca and Bénard have reported occasional instances of bradycardia in cases of nongangrenous appendicitis, this does not detract from Kahn's observation.

Because of the experience with our reported case, we should like to direct attention to and reëmphasize the importance of Kahn's observation, namely that bradycardia occurring in association with abdominal symptoms indicative of appendicitis, is very suggestive of gangrenous appendicitis.

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PERIARTERITIS AND ARTERITIS OF THE TEMPORAL VESSELS; A CASE REPORT*

By JOHN A. MACDONALD, M.D., F.A.C.P., and ROLLIN H. MOSER, M.D.,
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ARTERITIS of the temporal vessels has recently been described as a new clinical entity by Horton, Magath and Brown.[1] A case presenting similar clinical and pathologic data is the basis for this report.

CASE REPORT

A married woman, white, aged 60, a housewife living in the country, entered the hospital March 1, 1935, because of pain in her temples, fever, sweats and general malaise. About five weeks before admission she had noticed a tender area in front of her right ear. A week later the left side of her face became swollen and tender to pressure. At this time she became aware that the temporal arteries were very prominent and red and very tender. Mastication was painful. General malaise and weakness were pronounced, and fever and sweats were present every night. She had had no recent acute infection or injury although she had been to a beauty parlor for a permanent wave a few weeks before the onset of her illness. Her past history was of no importance. She had been exceptionally free of respiratory and gastrointestinal disorders. She had never had rheumatism, typhoid fever or malaria. There were no genitourinary symptoms. The menopause had occurred 12 years before. There had been a moderate weight loss of six pounds during this illness. Her father died from cerebral hemorrhage at sixty. She gave no history of previous vascular disease.

Physical examination revealed the left temporal artery to be very prominent from a point just above the temporomandibular joint for a distance of about two and a half inches. It was thickened, tortuous, the caliber irregular and the surrounding tissue very hyperemic. Pulsation was present throughout the course of the vessel at the time of the first examination although this became very much diminished a little later. There were no palpable nodules present. The right temporal artery was less acutely involved than the left but pulsation was definitely diminished. The preauricular and postauricular glands were moderately enlarged and tender. The right facial artery was somewhat indurated where it crossed the mandible but no other peripheral vessels were involved. The pupils reacted normally to light and in accommodation. Both nerve heads appeared normal and the retinal vessels showed about the usual change for her age. Two teeth were found to have definite periapical infection. The lungs were normal to physical examination. The heart was not

* Received for publication August 17, 1936.

grossly enlarged, a moderate tachycardia was present and a slight accentuation of the aortic second sound. A definite pulsation was felt in the suprasternal notch. The blood pressure was 148 systolic and 90 diastolic. A careful search of the skin and mucous membranes revealed no petechiae. The reflexes were intact and normal throughout and the vibration sense normal. The spleen and liver were not palpable and there were no masses, no fluid and no tender areas in the abdomen. Digital examination of the pelvis and rectum was negative. The average of several blood counts was as follows: Hemoglobin 71 per cent; red blood cells 3,580,000; white

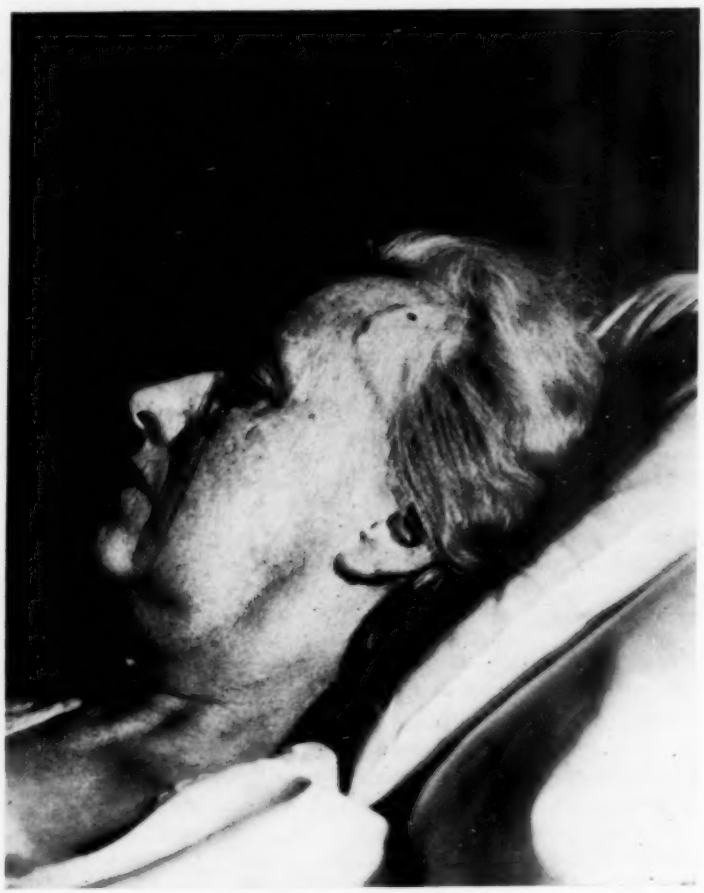

FIG. 1.

blood cells 8,600; with a normal differential. The coagulation and bleeding times and the platelet counts were normal. The Wassermann test was negative. Two blood cultures were negative. Agglutination tests for undulant fever, typhoid and paratyphoid were all negative. Several urine specimens at the time of admittance contained a faint trace of albumin and an occasional hyalin and granular cast; later specimens were negative. The phthalein test was 59 per cent in two hours and the urea clearance was 52 c.c. The basal metabolic rates were minus five and three. Roentgen-ray of the chest revealed a normal sized heart and a mild fibrosis throughout both lung fields. The temperature ranged from normal to 101.8° F. with

a very irregular curve. The pulse rate varied from 90 to 120. At no time were there any abdominal symptoms, peripheral nerve pains or involvement of the joints. The patient was kept at rest in bed and hot moist compresses of magnesium sulphate solution were applied to the temporal arteries. Sodium salicylate and Lextron were given orally. On March 29, a section of the right temporal artery three centimeters in length was removed. Cultures were made of the tissue on various types of media and sections made for histological study. The microscopic examination made by Dr. H. M. Banks was reported as follows: "Sections taken through four levels of the cross section of the temporal artery show a structure which is almost devoid of lumen. The intima is markedly hypertrophied, narrowing the lumen to a very small

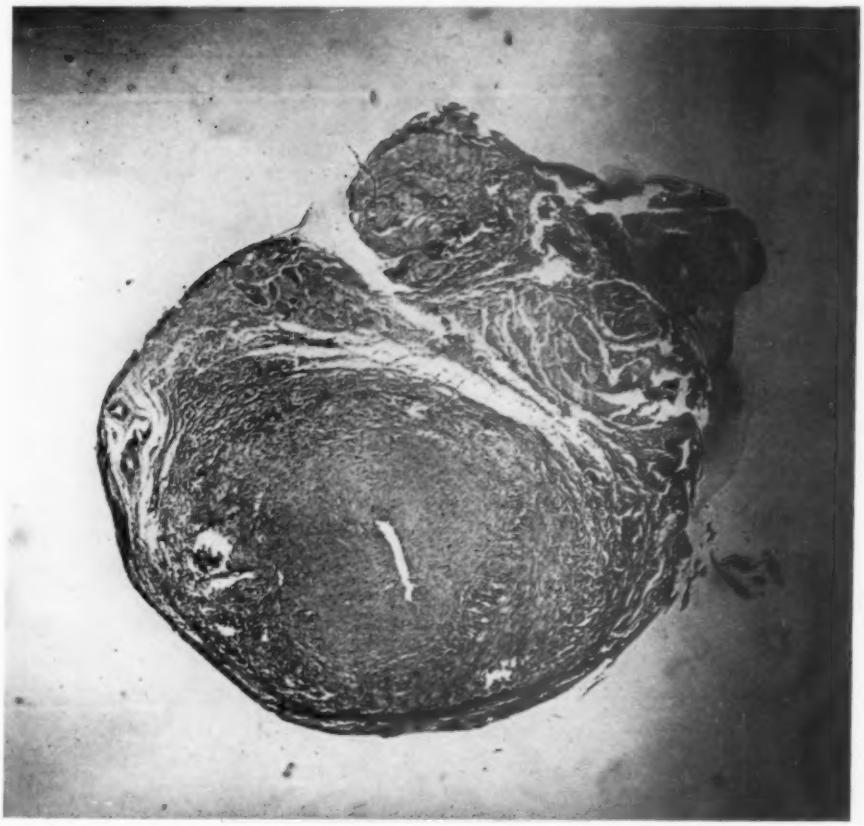

FIG. 2. Low power showing temporal artery characterized by (1) narrowing of lumen, (2) massive hypertrophy of vessel wall, (3) edema of connective tissue surrounding the arterial wall and inflammatory cell infiltration of this connective tissue.

point. The structure is homogeneous, somewhat hyalinized, and there is rather a scarcity of nuclear elements in the intima. The media shows almost total destruction and replacement by inflammatory cells of fibroblastic variety and by cicatrix formation. Immediately upon the exterior border of the media one finds in certain zones huge cells, irregularly round in contour, possessing many nuclei. These have the appearance of multinuclear native giant cells. The adventitia is quite narrow and atrophic in general appearance. The vasa vasorum shows hypertrophy of the muscular walls with some round cell infiltration. Cultures made from the specimen removed yielded a growth of *Staphylococcus aureus*."

It would seem significant that following the removal of this segment of diseased artery the temperature became normal and remained so until the patient left the hospital a week later. About one week after leaving the hospital there was a recurrence of fever but no local symptoms. The patient returned to the hospital on May 13 for examination. She had gained considerably in strength and her general appearance was much improved. She had had no fever after the first week. The incision over the right temporal artery was healed. The left temporal artery was smaller although it still showed evidence of inflammation. Pulsation was absent. There were no subcutaneous nodules, the eyegrounds were normal and the spleen not palpable. The remaining physical findings were the same as on the first admittance. The blood count had not changed and several specimens of urine were normal. The electrocardio-

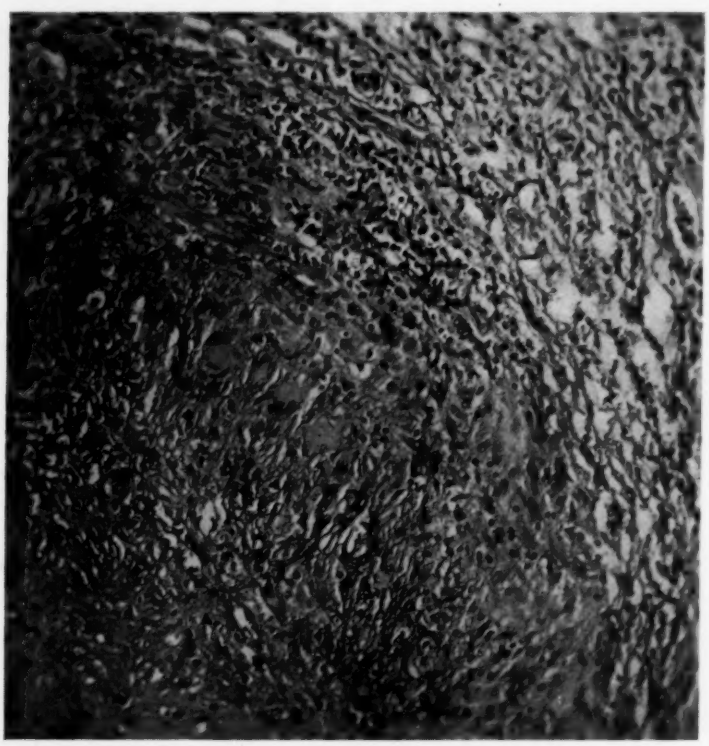

FIG. 3. Showing multinucleated giant cell formation in adventitial tissue inflammatory reaction.

gram was essentially normal. The blood pressure was 166 systolic and 86 diastolic. There was considerable pulsation in the suprasternal notch. A rather extensive pocket was found about one tooth and culture yielded *Streptococcus viridans*. The temperature ranged from normal to 99.6° and the pulse rate from 90 to 130. After dental extractions the patient left the hospital on May 17, 1935. She was seen again August 6, 1935, at which time she stated she felt very well in every way. The blood pressure was 160 systolic and 110 diastolic. The left temporal vessel appeared normal and there was a normal pulsation present. At this time there appeared to be increasing narrowing of the retinal vessels and more pulsation in the suprasternal notch. Our impression at this time was that she presented evidence of a mildly progressive vascular sclerosis. Examination in June 1936 revealed essentially the same findings as the year before. No local recurrence was noted.

In making a final diagnosis in this case one must consider periarteritis nodosa and a localized periarteritis as described by Brown. The clinical course and the histologic picture do not appear to closely simulate periarteritis nodosa. The description of this generalized arterial disease as given in the writings of Kussmaul,[2] Gruber,[3] Rothstein,[4] Wiener,[5] Lindberg,[6] Singer,[7] Friedberg and Gross,[8] Curtis and Coffey,[9] Hauser,[10] Barnard and Burbury,[11] Manges and Baehr [12] and others is that of a widespread involvement of the smaller vessels of the kidneys, heart, lungs, pancreas, mesentery, nerves, muscles and subcutaneous tissues. Since our patient presented no symptoms which might lead one to think of a generalized involvement we were more interested in those cases of arterial disease which presented subcutaneous lesions. Herlitz [13] reported superficial

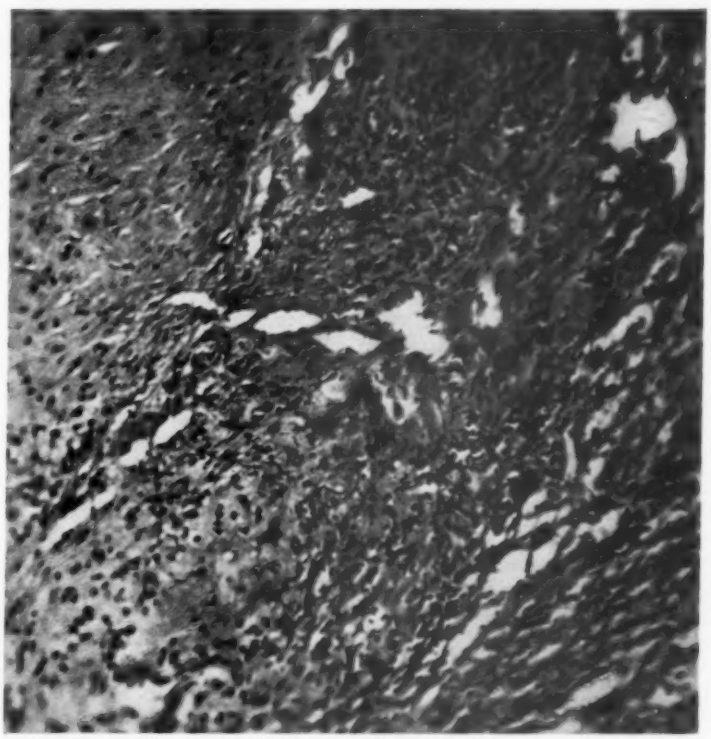

FIG. 4. Showing the small round cell diffuse infiltration of media and adventitia, also fibroblastic cell reaction.

nodules in 12.5 per cent of his cases of periarteritis nodosa. Lindberg [6] presented in detail a case of a young girl who apparently recovered after several exacerbations of joint pains, fever, anemia and numerous subcutaneous nodules which on section proved to be typical examples of periarteritis nodosa. He also reviewed 20 cases from the literature all being very similar in clinical and pathological detail. We could find no resemblance to our case in any of these.

CONCLUSION

A case is presented of localized arterial disease involving the temporal arteries which appears to be separate and distinct from the generalized condition of periarteritis nodosa.

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EDITORIALS

THE MEETING AT ST. LOUIS

THE Twenty-first Annual Session of the American College of Physicians at St. Louis was in every way a very successful meeting. The total registration, 2,321, places it as the second in size of attendance among all gatherings of the College up to this time. This figure has been surpassed only at the Philadelphia meeting in 1933 where 2,444 were registered. Moreover it was noteworthy that a very large proportion of those in attendance remained until the closing day.

Of the Regents of the College 21 out of 23 were present; and 49 of the 57 Governors either attended or sent representatives.

Throughout the meeting the large hall which housed the General Sessions was almost completely filled each afternoon. The Morning Lectures also drew a large attendance. The Round Table Discussions at the noon hour were an innovation in the program this year. They proved a most popular feature; more than four times the available number of tickets were applied for.

The clinical program provided by the hospitals and medical schools was of an unusually even grade of excellence. Seldom has more enthusiasm been expressed by the members than was brought out in discussions of these carefully arranged clinical meetings. They remain in the minds of the majority the most valuable single feature of our annual session.

St. Louis through its medical representatives greeted the College with warm and gracious hospitality and spared no pains in careful preparation for our reception. All who attended will look back with pleasure upon the days spent in the care of such thoughtful hosts and will hope that they will feel repaid by the gratitude of our members and the manifest success of their undertaking.

THE ANNIVERSARY VOLUME IN HONOR OF DR. JOSEPH HERSEY PRATT

IN this number of the ANNALS OF INTERNAL MEDICINE there appears a group of articles surmounted by a heading which indicates that they are contributed as the writers' part of an Anniversary Volume in honor of Dr. Joseph Hersey Pratt.

Dr. Joseph Hersey Pratt of Boston, who is widely known among the medical men of this country, will reach his sixty-fifth birthday this year. It was the desire of a large number of his friends to honor this occasion by the presentation to him of an Anniversary Volume. It was his own wish that the valuable contributions to be made to this volume should not be

barred from publication elsewhere as well, in a journal which would ensure their accessibility to the general medical public.

By agreement with the Committee in charge of the Anniversary Volume the Annals will publish in the coming months such articles contributed as are judged by the Editor to fall within the field of this journal. This plan, it is felt, will bring before our readers many interesting papers and will at the same time increase the permanent value of these contributions. It is an added pleasure to the Board of Editors that through this arrangement the ANNALS is of service to those who are responsible for this signal honor to an eminent physician.

REVIEWS

Urological Roentgenology. By MILEY B. WESSON, M.D., and HOWARD E. RUGGLES, M.D. 269 pages; 24 × 15.5 cm. Lea and Febiger, Philadelphia, Pa. 1936. Price, $5.00.

Urological Roentgenology is a small volume "prepared to meet the needs of the physician who wants to learn to interpret urograms." It is a 269 page book with 227 engravings. There are interesting chapters dealing with the history of urography and its detailed technic in the beginning, while the rest of the book is devoted to the diagnosis and interpretation of urograms covering the entire urogenital tract. The illustrations are excellent and not only useful, but essential in arriving at diagnoses of conditions in this tract.

Intravenous pyelography is discussed and depicted, its value and limitations are brought out carefully in contra-distinction to retrograde pyelography. Some very unusual pyelo-ureterograms of anomalies are shown indicating how easy it is for abnormal organs to undergo pathological changes. Also how essential it is to know the exact status of the upper urinary tract before surgery is undertaken, for example, it is necessary to know that there are *two* kidneys before removing *one*.

The usual pathological conditions of the kidney are well shown by pyelograms with descriptive footnotes. Many of the rare conditions, such as echinococcal cysts and actinomycosis of the kidney are also included.

The chapter on traumatism of the urinary tract suggests helpful methods by which the extent of the injury as well as the part of the urinary tract involved may be determined. Neurological lesions involving the urinary tract are also discussed.

While this book is of unquestioned merit, still it must be borne in mind that no two pathological conditions of the urinary tract are the same and for this reason no two urograms are the same, so diagnoses of urograms may be extremely difficult of interpretation. In other words, urograms must be regarded only as additional diagnostic information and not the sole dependency. If the physician regards this volume in this light it should be helpful.

W. H. T.

A Hand-Book of Ocular Therapeutics. By SANFORD R. GIFFORD, M.D. Second Edition. 341 pages; 20.5 × 14 cm. Lea and Febiger, Philadelphia, Pa. 1937. Price, $3.75.

It is with pleasure that we welcome a second edition of this monograph on Ocular Therapeutics. The work has been enlarged from 272 pages to 341 pages. Additions have been made in the field of vitamin and food therapy and also in that of the use of the various internal secretion extracts in the field of ophthalmology.

The application of the different means of physical therapy and the evolution of their use has also been brought up to date. The correction of an error in the table for tuberculin dilutions will be welcomed by those using the book as a guide in this type of work. The reviewer feels that an initial dose of 1/50,000 mgs. of tuberculin as recommended for treatment of a retinal lesion is far too great and may cause very definite damage in a few very sensitive patients.

The author and publishers are to be commended for this excellent work which can be recommended as a guide both for the ophthalmologist and the general man who may be called upon to render service in many eye conditions.

C. A. C.

The Clinical Use of Digitalis. By DREW LUTEN, M.D., Associate Professor of Clinical Medicine, Washington University School of Medicine. Indexed. 226 pages; 23.5 × 15.5 cm. Charles C. Thomas, Springfield, Ill. and Baltimore, Md. 1936. Price, $3.50.

The more recent explanations of the pharmacological and clinical action of digitalis are presented in this volume. The author emphasizes that the clinical indication for the use of this drug is primarily congestive heart failure, no matter what the heart rythm may be. He also points out that its continued use tends to prevent subsequent failure in a heart which has failed at one time. It would seem to be of use in preventing failure, when such a state might be assumed to be imminent. The reviewer highly recommends this book to practitioners, especially that part which deals with the clinical use of digitalis. As regards some of the considerations of the mode of action of digitalis, at times the argument seems more specious than convincing.

W. S. L., JR.

A Text-Book of Neuro-Anatomy. By ALBERT KUNTZ, M.D. Second Edition. 519 pages; 24 × 16 cm. Lea and Febiger, Philadelphia, Pa. 1936. Price, $6.00.

This book is a straight-forward presentation of facts in text book form. It avoids discussion of debatable subjects, and bibliographic references are to all intents and purposes completely absent in the text though a short list of collateral subject matter is found at the end of each chapter. With this set up the author has been able to cover an astonishing breadth of field in a medium sized text. Thus phylogeny and embryology are featured as an introduction and the embryology of the brain is further discussed in the section dealing with the brain.

The usual sequence of presentation is followed, consideration of neural histology and morphology preceeding the detailed internal structure of the central nervous system. The latter is attacked in the order of spinal cord, brain stem and cerebellum and finally the forebrain. Each subtitle, a.e., the cranial nerves, ends with a short, but not too short, summary of the subject.

The subject matter is brought up to date, particularly that featuring Cannon's fundamental contributions to the physiology of the autonomic system. The analysis of the cerebral cortex is clear, concise and convincingly illustrated—an altogether useful presentation. A similar success in dealing with the basal nuclei is conspicuously lacking; one leaves this subject with a scant grasp of the significance of these centers.

The clear and abundant illustrations are enriched by numerous Nissl preparations of nuclear areas, a visual asset all to often neglected in this type of work.

Clinical application of neuro-anatomy is presented through description of a series of representative lesions of the nervous system with an analysis of their significance. The book ends with a concise laboratory manual of the dogfish and human brain. One may term this a useful and practical presentation of a difficult subject.

C. L. D.

The Practitioner's Library of Medicine and Surgery. Supervising Editor, GEORGE BLUMER, M.A. (Yale), M.D., F.A.C.P.; David P. Smith Clinical Professor of Medicine, Yale University School of Medicine; Consulting Physician to the New Haven Hospital. *Volume XI: Eye, Ear, Nose and Throat.* Associate Editors ARTHUR M. YUDKIN, M.D., Clinical Professor of Ophthalmology, Yale University School of Medicine; and PAUL B. MACCREADY, M.D., F.A.C.S., Assistant Clinical Professor of Otolaryngology, Yale University School of Medicine. Lxvii + 1153 pages, 402 illustrations. 25 × 17 cm. D. Appleton-Century Company, New York. 1937. Price, $10.00 a volume.

The eleventh volume of *The Practitioner's Library*, like its predecessors which have been reviewed from time to time in the ANNALS, relates the essential material of certain special phases of Medicine to the experiences of the clinician in his daily practice. Thus it presents those diseases of the *Eye, Ear, Nose and Throat* which the general practitioner may encounter at any time, which he can diagnose, and which, for the most part, can be treated adequately by standard, proved methods and with the means readily available to the physician who has a large and varied group of patients. Diagnosis and treatment are emphasized. When major operative procedures are discussed it is with the thought of giving the practitioner such background material as will make it proper for him to advise his patients as to what may properly be expected from those who are recognized specialists in the field in question. This volume, therefore, presents that material which is more or less constantly needed by every practitioner, and which he must have available if he is to serve his clientele adequately in respect to the affections of the special sense organs and related structures.

To this volume there have been 43 contributors, chosen largely from the younger workers in these special fields. The subject matter is divided into four main parts, with about 385 pages devoted to diseases of the Eye, 275 to the Ear, 250 to the Nose, 125 to the Pharynx and 90 to the Larynx. Numerous, and usually well-chosen, illustrations are utilized throughout. Considering the avowed purpose of the book, it must be questioned whether the space occupied by the many low-power photomicrographs in chapter XVII, dealing with the histopathology of the ear, could not have been used to better advantage otherwise. Although obviously prepared from beautiful specimens, such figures require considerable expert knowledge for their appreciation.

As the reviewer has had occasion to mention in respect to earlier volumes of this series, typographical slips are very few for a first edition. A misspelled word in a running head throughout chapter XLV, will offend the eye of a critic, no matter how kindly disposed he may be. The general press work is excellent, the binding substantial and attractive and the index adequate. It is impossible to evaluate the individual chapters provided by the many contributors, but the work as a whole is a worthy member of this series, and will prove a valuable aid to every practitioner of Medicine.

C. V. W.

Being Born. By MRS. FRANCES BRUCE STRAIN, Associate Educational Director, Cincinnati Social Hygiene Society. Cloth. Price, $1.50. Pp. 144, with 28 illustrations. New York & London: D. Appleton-Century Co., 1937.

This book is written by a mother for her children, and covers all the essentials on the subject of human reproduction. It is written especially for the pre-adolescent boy and girl, and is presented in a very sane and healthy manner. There are twelve chapters and "a list of words and their meanings." Most of the material is in the form of questions and answers, which is the best way of presenting the subject to children.

This book can be highly commended for avoiding the abnormal, which unfortunately is introduced in most books on sex, even for children. A few parents might hesitate to tell their children about coitus, or as Mrs. Strain says "mating is not only a way to start one's family, but is also a way of expressing their love, husbands and wives unite when no baby is to be started," but her discussion of this subject cannot cause offense.

The author has covered almost every question that a normal, questioning and curious youngster might ask. She does not beat about the bush, tells how, why, and where babies come into being. The physician certainly can recommend this book to all parents.

J. L. McC.

COLLEGE NEWS NOTES

Nominating Committee for 1937–38

In accordance with Article I, Section 3, of the By-Laws of the American College of Physicians, the President, Dr. J. H. Means, has appointed the following Nominating Committee for 1937–38:

Dr. Jonathan C. Meakins, Montreal, Que., *Chairman;*
Dr. James B. Herrick, Chicago, Ill.;
Dr. Alexander M. Burgess, Providence, R. I.;
Dr. A. Comingo Griffith, Kansas City, Mo.;
Dr. William R. Houston, Austin, Tex.

The first two names are appointments from the Board of Regents; the second two names are appointments from the Board of Governors; the last name is an appointment from the Fellowship at large.

New Life Member

Dr. Estella G. Norman (Fellow), Miami Springs, Florida, became a Life Fellow of the American College of Physicians on April 27, 1937.

Books

Dr. James H. Means (Fellow), Boston, Mass., "The Thyroid and its Diseases";
Dr. Ralph Pemberton (Fellow), Philadelphia, Pa., "Arthritis and Rheumatoid Conditions";
Dr. William R. Houston (Fellow), Austin, Tex., "The Art of Treatment";
Dr. William Gerry Morgan (Fellow), Washington, D. C., "Functional Disorders of the Gastro-intestinal Tract."

Reprints

Dr. H. Sheridan Baketel (Fellow), Jersey City, N. J.—1 reprint;
Dr. Grafton Tyler Brown (Fellow), Washington, D. C.—1 reprint;
Dr. C. T. Burnett (Fellow), Denver, Colo.—15 reprints;
Dr. A. Morris Ginsberg (Fellow), Kansas City, Mo.—1 reprint;
Dr. Jacob Gutman (Fellow), Brooklyn, N. Y.—1 copy, tenth supplement to "Modern Drug Encyclopedia";
Dr. Arthur M. Master (Fellow), New York, N. Y.—2 reprints;
Dr. Sydney R. Miller (Fellow), Baltimore, Md.—1 reprint;
Dr. Kenneth Phillips (Fellow), Miami, Fla.—1 reprint;
Dr. William R. Rawls (Fellow), New York, N. Y.—1 reprint;
Dr. Paul H. Ringer (Fellow), Asheville, N. C.—1 reprint;
Dr. Felix J. Underwood (Fellow), Jackson, Miss.—1 reprint;
Dr. L. B. Carruthers (Associate), Miraj, India—1 reprint ;
Dr. George B. Dorff (Associate), Brooklyn, N. Y.—8 reprints;
Dr. Stuart L. Vaughan (Associate), Buffalo, N. Y.—1 reprint;
Dr. Walter A. Bastedo (Fellow), New York, N. Y.—3 reprints;
Dr. A. B. Brower (Fellow), Dayton, Ohio—1 reprint;
Dr. A. Allen Goldbloom (Fellow), New York, N. Y.—2 reprints;
Dr. Charles H. Lutterloh (Fellow), Hot Springs, Ark.—2 reprints;
Dr. Philip B. Matz (Fellow), Washington, D. C.—1 reprint;
Dr. Oliver T. Osborne (Fellow), New Haven, Conn.—1 reprint;

Dr. Joseph F. Painton (Fellow), Buffalo, N. Y.—5 reprints;
Dr. Paul A. Draper (Associate), Colorado Springs, Colo.—2 reprints.

Meeting of Southern California Members

Seventy-five of the Southern California members of the College held a dinner meeting at the California Club, Los Angeles, on March twentieth, 1937. Dr. Egerton L. Crispin, former Governor and present Regent of the College, presided. Dr. F. M. Pottenger, ex-president, spoke upon the certification of internists and other matters pertinent to the College; Dr. Wm. J. Kerr, San Francisco, now president-elect of the College, delivered an interesting address upon the future of the College in the advancement of medicine.

Testimonial Dinner to Dr. Riesman

Dr. David Riesman (Fellow) was guest of honor at a dinner on the evening of March 25, 1937, at the Bellevue-Stratford Hotel, Philadelphia, attended by more than two hundred and fifty of his professional friends on the occasion of his seventieth birthday. Guest speakers included Provost Josiah Penniman of the University of Pennsylvania, Dr. Alfred Stengel (Master), Dr. Henry A. Christian (Fellow) of Boston, Dr. Lewis A. Conner (Fellow) of New York City, Dr. Wilmer Krusen of the Philadelphia College of Pharmacy and Science, Dr. Wm. Gerry Morgan (Fellow) of Washington, and Dr. Walter C. Alvarez (Fellow) of Rochester, Minn. Dr. Russell Boles (Fellow) of Philadelphia was toastmaster. Dr. Stanley C. Harris announced that friends of Dr. Riesman had made possible the publication of a volume of his selected writings to celebrate his birthday. An engraved plate, bearing the names of Dr. Riesman's former and present assistants, was presented by Dr. Thomas FitzHugh, Jr. (Fellow). Dr. Riesman responded with a characteristically delightful account of his medical career and of his view of the present and future of medicine envisioned from the vantage point of his "seventy-year-high mountain top."

Dr. Albert E. Russell (Fellow), U. S. Public Health Service, Washington, D. C., gave the Second Annual Harold S. Boquist Memorial Lecture at the University of Minnesota Medical School, Minneapolis, on December 6, 1936.

The Annual Meeting of the California Tuberculosis Association was held at Riverside, California, April 1–3, 1937. Dr. R. H. Sundberg (Fellow), San Diego, was chairman of the program committee; Dr. F. M. Pottenger (Fellow), Monrovia, was vice president; Dr. Chesley Bush (Fellow), Livermore, Dr. R. L. Cunningham (Fellow), Los Angeles, and Dr. W. C. Voorsanger (Fellow), San Francisco, were directors of the Association. Dr. Sidney J. Shipman (Fellow), San Francisco, acted as chairman of one of the clinical sections, and discussed the paper on bronchial stenosis. Dr. Robert A. Peers (Fellow), Colfax, presented a paper on "Routine Tuberculin Testing in Schools: The Part Played by the Medical Profession"; Dr. Lyell C. Kinney (Fellow), San Diego, presented a paper on "Diagnosis of Tuberculosis of the Intestinal Tract"; Dr. Munford Smith (Fellow), Los Angeles, presented a paper on "Relationship of Trauma to Tuberculosis," said paper being discussed by Dr. Philip H. Pierson (Fellow), San Francisco, and Dr. R. L. Cunningham (Fellow), Los Angeles; Dr. Carl R. Howson (Fellow), Los Angeles, presented a paper on "Differential Diagnosis of Diseases of the Chest," said paper being discussed by Dr. Munford Smith (Fellow), Los Angeles, and Dr. Harold G. Trimble

(Fellow), Oakland; Dr. Harold G. Trimble (Fellow), Oakland, with Dr. B. H. Wardrip, presented a paper on "Pneumoperitoneum—Its Use in Pulmonary Tuberculosis," said paper being discussed by Dr. E. W. Hayes (Fellow), Monrovia; Dr. Philip H. Pierson (Fellow), San Francisco, discussed the paper on "Simultaneous Bilateral Pneumothorax in the Treatment of Pulmonary Tuberculosis."

The Tenth Annual Graduate Fortnight of the New York Academy of Medicine will be held November 1–12, 1937, and will be devoted to a consideration of medical and surgical disorders of the urinary tract. The subject will include Bright's disease, arterial hypertension, and infections, tumors, calculi and obstructions of the urinary tract, and will exclude venereal disease and gynecology. For the Annual Fortnight a subject of outstanding importance in the practice of medicine and surgery is selected and is presented from as many angles as possible.

The program is under the general direction of the Committee on Medical Education. The following Fellows of the College are members of this Committee: Dr. Walter P. Anderton, Dr. F. Warner Bishop, Dr. Ralph H. Boots, Dr. Arthur F. Chace, Dr. Emanuel Libman, Dr. Thomas T. Mackie, Dr. Herman O. Mosenthal, Dr. Bernard S. Oppenheimer, Dr. Maximilian A. Ramirez, Dr. Willard C. Rappleye, Dr. Howard F. Shattuck, Dr. Charles F. Tenney and Dr. John Wyckoff.

Dr. Ralph Pemberton (Fellow), Philadelphia, delivered a series of lectures on "The Modern Outlook upon Arthritis," including the Hartford (Conn.) Medical Society on April 5, the Lycoming County (Pa.) Medical Society at Williamsport, Pa., on April 9, and the New Castle County (Del.) Medical Society at Wilmington, Del., on April 20. Dr. Pemberton also addressed the Health Institute sponsored by the Women's Auxiliary of the Philadelphia County Medical Society on April 13 on "Arthritis; and the Problem of Control."

Dr. Anthony C. Cipollaro (Associate), New York City, has been recently appointed consulting dermatologist at the St. Joseph's Hospital of Far Rockaway.

OBITUARIES

DR. CHARLES VINCENT NIEMEYER

Dr. Charles Vincent Niemeyer, Fellow, 4610 Hudson Boulevard, Union City, N. J., died January 11, 1937, of myocarditis following a collapse in his office six weeks before, at the age of 48.

Dr. Niemeyer, the son of Carl H. and Katherine Niemeyer, was born in New York City, March 7, 1888. He attended public and private school in New York City, and graduated from the University of Vermont, M.D., 1912. He served as Interne in Red Cross and St. Vincent's Hospital and five years years in St. Mary's Children Clinic in New York City. In 1914 he moved to Union City, N. J., where he began the practice of his profession. In the same year he began the first Baby Welfare Station in North Hudson County, and established seven Baby Stations in Monmouth County in 1919. He limited his practice to Pediatrics in 1917, being the first in North Hudson County to do so.

In 1929–32 he did post-graduate work in Vienna, Berlin, London, Mt. Sinai of New York, Boston and Chicago.

Rejected during the World War, he organized a Red Cross Chapter for North Hudson and devoted much effort to it. He was a Charter Member of North Hudson Physician's Society, acting as President for one term and as Secretary for fifteen years. He was a member of Osler Medical Society, Hudson County Medical Society, New York Academy of Medicine, New Jersey State Medical Society, American Pediatric Society, American Medical Association, and a Fellow of the American College of Physicians since 1931.

At the time of his death, he was Chief of the Pediatric Staff, St. Mary's Hospital, Hoboken, N. J.; Consultant to St. Mary's Hospital and Attending Physician to North Hudson Hospital; Consultant to Christ's Hospital, Jersey City, and to Nyack General Hospital.

He was a member of St. Augustine Church, Fourth Degree Knight of Columbus, member of the Newman Club, Kiwanis Club and the Nu Sigma Nu Medical Fraternity. In 1920 he married Caroline Salenius, who survives him.

In so short a span of life, he accomplished much. The Community and the Profession have suffered a great loss in his untimely death.

CLARENCE L. ANDREWS, M.D., F.A.C.P.,
Governor for New Jersey.

DR. WILLIAM LAFAYETTE RICH

Dr. William Lafayette Rich (Fellow), Salt Lake City, Utah, died November 17, 1936, of chronic myocarditis; aged, fifty-eight years.

Dr. Rich was born June 17, 1878, at Montpelier, Idaho, and for a number of years had followed the specialty of dermatology. He attended the

Weber State Academy, Ogden, Utah, and the Bear Lake Academy, Paris, Idaho, and later, the Utah Agricultural College at Logan, Utah. He was graduated from Washington University School of Medicine, St. Louis, in 1907, and was certified by the American Board of Dermatology, June 11, 1934. He had pursued postgraduate study at the London Hospital Medical College (University of London), Middlesex Hospital, London, Charing Cross, St. Barth, St. Mary's and other London institutions. In addition, he did postgraduate work at the Vanderbilt Clinic, New York City, and at the New York Postgraduate Medical School.

For several years, Dr. Rich had been chief of the Dermatological Clinic, Salt Lake General Hospital; dermatologist, Dr. W. H. Groves Latter-Day Saints Hospital, St. Mark's Hospital, the U. S. Veterans Administration Facility, and the D and R–G and Western Pacific Railway. He was a Captain, Medical Officers Reserve Corps, and during the World War was a member of the National Advisory Board. He was a former president and a former secretary of the Utah State Medical Association, and a member of the House of Delegates of the American Medical Association in 1923. Dr. Rich had been an active and interested Fellow of the American College of Physicians since 1920.

Dr. Rich was one of the best liked physicians by his colleagues in his city. He had always been active in medical society affairs and enjoyed a large consultant practice up to the time of his death. One of his chief characteristics was that he served as a peace maker. He took an active interest in child welfare work. He will be mourned by many patients as well as by his colleagues.

L. E. Viko, M.D., F.A.C.P.,
Governor for Utah.

DR. B. H. FRAYSER

Benjamin Hobson Frayser; born, Buchanan, Va., October 7, 1887; attended public schools of Charlottesville, Va., Cleveland's Private School, Pantops Academy, Va., and the Fisburne Military School, Va.; three years, Baltimore Medical College (now University of Maryland); M.D., Lincoln Memorial University Medical Department (now University of Tennessee), 1909; Ph.G., University of the South, 1909; Interne, Pottsville (Pa.) Hospital and Chicago Lying-in Hospital; for a time connected with the Soldiers' Home Service Hospitals at Grand Rapids, at Dayton, Ohio, and at Hot Springs, S. D.; also Associate Professor of Obstetrics and Instructor in Anatomy, Lincoln Memorial University; also Associate Professor, Pharmacology, University of the South; Resident Physician, Santo Tomas Hospital, Panama City, 1914–15; in 1915 entered U. S. Indian Medical Service and was in charge of health work in San Juan Hospital, Shiprock, N. M., and Government Hospital, Dulce, N. M., until 1920; from July, 1920, Passed Assistant Surgeon (R) in the following U. S. Public Health Service

Hospitals—New Haven, Connecticut, Boston, Mass., Helena, Mont., and Lexington, Ky.; at time of death, Senior Medical Officer, in charge of medical and surgical sections, U. S. Veterans Administration Facility, Lexington, Ky.; founder, Pi Delta Pi Secondary School Fraternity; member, Chi Zeta Chi, medical fraternity; Kappa Phi, pharmaceutical fraternity, Sigma Phi Epsilon and Theta Nu Epsilon fraternities; ex-President, the Association of Government Surgeons of the United States; member, American Medical Association, Association of Government Surgeons, Medical Veterans of the World War, National Reconstruction Alliance, Sons of the American Revolution, Veterans of Foreign Wars; Fellow of the American College of Physicians since March 10, 1923; author of several published papers, and former Business Manager of *The Indian Medical News*.

The following information has been supplied by Dr. Jo M. Ferguson of the Veterans Administration, Lexington, Kentucky, who has been closely associated with Dr. Frayser since March 16, 1931.

"Dr. Frayser was very painstaking in his work, always kind and courteous to the patients in his charge, as well as to all of the personnel with whom he was associated. There was not a physician in the hospital better liked or who was more trusted by every one than Dr. Frayser. He was always genial and pleasant and willing at all times to do the most he could for his associates. He was never too busy to listen to complaints of patients and employees and to give of his time and the benefit of his training and experience to those in need of aid or advice. He was always loyal to his fellow workers and had the love and admiration of all those with whom he was associated, and his death on March 5, 1937, has been keenly felt by all."

C. W. Dowden, M.D.,
Governor for Kentucky.

DR. RANDOLPH L. McCALLA

Dr. Randolph L. McCalla, an Associate of the College, Boise, Idaho, died October 10, 1936, of uremia, aged forty years. He was born and reared in Boise, the son of the late Dr. L. P. McCalla.

Dr. McCalla received his A.B. degree from Georgetown University, Washington, D. C., in 1916, then took two years in medicine at Harvard University, and received his degree in medicine from Columbia University College of Physicians and Surgeons in 1920. He was an interne at St. Agnes Hospital, Baltimore, 1920–21, and thereafter, successively, assistant in medicine, instructor in medicine, assistant professor in medicine and chief of the medical clinic at the University of California Medical School, 1924–29. He was house officer in the San Francisco Hospital during 1924–25, and resident physician in the University of California Hospital, 1925–27; assistant visting physician in the same institution, 1925–29; resident physician, Laguna Honda Home, San Francisco, 1927–29. He then went to

Hawaii, where he was physician-in-charge, Lanai Plantation Hospital, 1930–34. He returned to Boise, Idaho, in May, 1936.

Dr. McCalla had been a member of the California Academy of Medicine, the Territorial Medical Society of Hawaii, and the American Medical Association. More recently, he had become a member of the local societies in Idaho. He was elected an Associate of the American College of Physicians during 1934.

He was the author of several published articles, dealing primarily with cardiology. He was a thoroughly capable internist of high integrity, possessed of an excellent medical mind, a credit to himself and to the organizations with which he was connected.